Hydrogen sulfide donors or related derivatives are the future medicines of renal diseases

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Hydrogen sulfide (H_2S) is one of the three gasotransmitters that possess anti-inflammatory, antiapoptotic, and antioxidant properties. It maintains the function of the kidney through its effect on the glomeruli and the renal transport system. Literature review using PubMed, Excerpta Medica database (EMBASE), Google scholar, and Cochrane review revealed that H_2S donors are introduced as exogenous H_2S and have been found to target many organs in in-vitro and in-vivo studies. This review provides the main research that was performed on the H_2S donors in the context of kidney disease. Exogenous H_2S supplementation can be administered in different therapeutic areas promising therapeutic strategy in the setting of kidney diseases. Therefore, suitable pharmaceutical preparations of H_2S donors are necessary to be launched in the markets for the prevention and treatment of acute/chronic renal diseases.

Keywords:
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Introduction

Hydrogen sulfide (H_2S) is a colorless gas, soluble in water and lipophilic solvents in a ratio of 1 : 5; this property explains its permeability across the plasma membrane. Its concentration under optimum physiological conditions ranged between 10 and 300 μmol/l. It is produced enzymatically in mammals from the sulfur-containing amino acids (e.g. l-cysteine) under the influence of cystathionone-β-synthetase (mainly in the brain), cystathionine-γ-synthase (mainly in the heart, blood vessels, kidney, and liver), and mercaptopyruvate sulfur transferase enzymes. This gas serves as a signaling molecule or gasotransmitter [similar to nitric oxide (NO) and carbon monoxide], and it behaves as oxygen sensor under ischemic conditions [1]. It is oxidized in the mitochondria to thiosulfate and sulfate by sulfide–quinone oxidoreductase, persulfide dioxygenase, rhodanese, and sulfite oxidase enzymes. It is removed from the body by means of desulfurization, cytosolic methylation, and sulfhemoglobin formation. The purpose of this study was to focus on the future of these H_2S donors on the renal diseases because these compounds exert a beneficial effect on the glomeruli and the transport system of the kidney. In addition, they have pleotropic effects such as anti-inflammatory and scavenging free radicals.

In this review, the data were collected from articles and reviews published in PubMed, Excerpta Medica database (EMBASE), Google scholar, and Cochrane review, taking into considerations their biological activity, mechanism of action, and possible indications of H_2S donors based on the experimental and clinical studies.

Biological actions of hydrogen sulfide

H_2S is involved in several vital processes in the body, including neuromodulation, proliferation of vascular smooth muscle cells, regulations of the systemic and pulmonary blood pressures, inflammation, edema, and hemorrhagic shock. It has antioxidant properties and is capable of reducing the oxidative stress by removing the reactive oxygen species (ROS). It participates in the regulation of the renal function, including the glomeruli and the tubular system. Its effect on the kidney was established in both physiological and pathological conditions through two possible mechanisms: (a) inducing vasodilation of the arteries through the activation of the potassium channel (K_{ATP}) and (b) counteracting the excessive production of ROS generated after renal tissue injury [1]. Low levels of H_2S reduce the production of hydrogen peroxide, superoxide anion (O_2^-), and peroxynitrite ($ONOO^-$), whereas high levels of H_2S play a role in the production of ROS and reactive nitrogen species. The other harmful effects of H_2S include the following.

(1) Induction of brain infarction [2]. In one experimental animal study, ligation of the

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middle cerebral artery resulted in the upregulation of cystathionine β-synthase enzyme accompanied with overproduction of H_2S and aggravation of neuronal cell death [3].
(2) Aggravation of the symptoms of Down's syndrome. Overproduction of endogenous H_2S was observed in Down's syndrome patients [4].
(3) Acceleration of atherosclerosis and induction of hypertension and coronary artery disease through its direct vasoconstrictor effect and suppression of the NO production [5,6].
(4) Induction of pulmonary hypertension [7].
(5) Aggravation of peptic ulcer and gastritis [8]. The expression of cystathionine-γ-lyase was found to be higher in patients with *Helicobacter pylori*-negative gastric ulcer than in those with *H. pylori*-positive gastric ulcer, and it is positively correlated with the expression of NF-κβ [8]. On the other hand, H_2S donors protect the gastric mucosal cells from injury induced by acetylsalicylic acid [9]. Therefore, endogenous and exogenous H_2S exerts a dual effect on the gastric mucosa.

Hydrogen sulfide donors

H_2S donors are classified according to their ability to release H_2S or with respect to their availability or the pharmaceutical preparations (Tables 1 and 2) as follows.

(1) Inorganic sulfide salts (e.g. NaHS, Na_2S).
(2) Synthetic organic slow-releasing H_2S donors (e.g. GYY4137).
(3) H_2S-releasing hybrid drugs (e.g. ACS15-diclofenac).
(4) H_2S precursors (e.g. cysteine analogs, nucleoside phosphorothioates).
(5) Plant-derived polysulfides in garlic.

Therapeutic targets of hydrogen sulfide donors

Previous studies highlighted the importance of H_2S in the pathogenesis of many diseases. Therefore, many systems and organs are the targets of H_2S donors as a therapeutic modality.

(1) Cardiovascular system: In hypertension, H_2S donors can reduce blood pressure and are able to protect the organs from damage [10]. In the experimental animal study, it was observed that H_2S donors protect the heart against ischemic–reperfusion (I/R) injury through the activation of the activated mitogen protein kinase enzyme pathway, thus restoring the autophagic flux [11]. There is evidence that atherosclerosis is associated with low endogenous levels of H_2S production, and that H_2S donor supplementation such as NaHS and GYY4137 may attenuate the atherosclerosis process [12]. H_2S donors may be the future therapeutic agents for heart failure. Current studies have shown that H_2S plays a role in the regulation of specific cardiac microRNAs and thereby ameliorates the cardiac dysfunction [13]. In peripheral artery disease, H_2S adversely affects the patients because it interferes with NO production. In one clinical study, it has been found that the plasma ratio of H_2S to NO was significantly higher in patients with peripheral artery disease [14].
(2) Central nervous system: H_2S donors (e.g. ADT-OH or NaHS) combined with tissue plasminogen activator significantly reduced the hemorrhage that followed the ischemic stroke [15]. The synthesis of brain H_2S is severely reduced in Alzheimer's disease patients, and the free plasma H_2S levels are inversely correlated with the severity of dementia. In an experimental animal study, H_2S donors, through several mechanisms, reduced the progression of dementia by assessing the cerebral

Table 1 Pharmacological actions of slow-releasing hydrogen sulfide donors

Pharmacological actions	Slow-releasing H_2S donors
Anti-inflammatory	GYY4137, ADT-OH, S-propargyl-cysteine, Lawesson's reagent
Antioxidant and free radical scavengers	ADT, ADT-OH, AP39, *N*-acetylcysteine, *N*-acetylcysteine ethyl ester, SAC, phosphorodithioates
Vasodilatation	GYY4137, thioamino acids, AP39, dithioperoxyanhydrides
Antithrombotic	GYY4137
Angiogenesis promotion	S-Propargyl-cysteine
Improve wound healing	4-Hydroxythiobenzamide
Target organ protection (cardio, neuro, and gastroprotection)	ADT, S-propargyl-cysteine, SG-1002, Lawesson's reagent, S-SH compounds, S-memantine, ACS1
Anticancer	GYY4137, S-propargyl-cysteine, ACS1
Under investigation	S-aroylthiooximes, arylthioamides, *N*-(benzoylthio)benzamides, PhNCS, PhNCS-COOH, thioglycine, l-thiovaline, *N*-(acetylthio)benzamides, H_2S photo-donor5, gem-dithiol compounds, allyl isothiocyanate, benzyl isothiocyanate, 4-hydroxybenzyl isothiocyanate, erucin, sinigrin, poly(ethylene glycol)-ADT

Table 2 Pharmacological actions of hydrogen sulfide-releasing hybrid drugs

Pharmacological actions	H_2S-releasing hybrid drugs
Anti-inflammatory	ACS15-diclofenac, ACS83-l-DOPA, ACS84-l-DOPA, ACS85-l-DOPA, ACS86-l-DOPA, ATB-337-diclofenac, ATB-343-indomethacin, ATB-345-naproxen, ATB-346-naproxen, ATB-429-meselamine, NOSH-aspirin, NOSH-naproxen (AVT-219), NOSH-sulindac (AVT-18A), S-diclofenac
Antioxidant and free radical scavengers	ACS6-sildenafil, ACS14-aspirin
Vasodilatation	H_2S-EXP 3174-active metabolite oflosartan
Improve vascular function	S-zofenopril
Proerectile	ACS6-sildenafil
Antithrombotic	ACS14-aspirin, compound 8e-3-n-butylphthalide
Antiangiogenesis	ACS2-valoproate, ACS15-diclofenac, ACS18-sulindac
Antiosteolysis	ACS32-diclofenac
Regulation of insulin release	ACS67-latanoprost
Target organ protection (cardio, neuro, gastroprotection)	ACS6-sildenafil, ACS14-aspirin, ACS21-salicylic acid, ACS84-l-DOPA, S-diclofenac
Anticancer	ACS2-valoproate, ACS15-diclofenac, ACS18-sulindac, ACS33-valoproic acid, ATB-346-naproxen, HS-acetylsalicylic acid, NOSH-aspirin

histopathological, biochemical, and immunological indices [16].

(3) Gastrointestinal tract: Tsubota and Kawabata [17] highlighted the implication of endogenous H_2S for the treatment of irritable bowel syndrome and the exogenous H_2S as with H_2S donors for the treatment of inflammatory bowel disease (e.g. Crohn's disease).

(4) Others: erectile dysfunction, organ transplantation, cancer, etc.

What are the reasons that make the hydrogen sulfide donors suitable medications for acute/chronic kidney diseases?

H_2S is a potential signaling molecule that protects the kidney from different harmful insults because it has the following biological effects.

(1) It has beneficial effects against the inflammatory process that is associated with kidney disease – complicated by chronic disorders such as rheumatoid arthritis, diabetes mellitus, and atherosclerosis by acting through the following mechanisms.
   (a) Improvement in renal blood flow [18] through the following mechanisms:
   (b) ATP-sensitive K^+ channels (K_{ATP}).
   (c) Upregulation of intracellular cAMP.

(2) Downregulation of the inflammatory and immune responses by the evidence of [19–21]:
   (a) Inhibition of activation of NF-κβ and p38 mitogen-activated protein kinase enzyme.
   (b) Inhibition of caspase-3 cleavage.
   (c) Downregulation of the proinflammatory markers including tumor necrosis factor α (TNF-α), interleukin (IL)-1β, IL-6, and IL-8.

(3) Scavenging the oxidants and reduced tissue injury by inducing apoptosis and/or scavenging the free radicals generated by neutrophils [22,23].

Therefore, H_2S donors (Table 1) are potentially useful in renal diseases, and previous studies implicated these agents in the following conditions.

Ischemic–reperfusion injury

One of the most common causes of acute kidney injury is renal I/R, which resulted from shock or complicated surgical procedures that follow kidney transplantation and resection [24–26]. H_2S plays a role in ameliorating renal I/R injury by the following effects: antioxidant, antiapoptotic, and anti-inflammatory effects [27–30]. Ibrahim *et al.* [31] demonstrated that NaHS protects the kidney from I/R injury by inhibiting the proinflammatory cytokines (TNF-α) and downregulating the expression of inducible NO synthetase enzyme and upregulating the endothelial NO synthetase enzyme. The mitochondria-targeted slow-releasing H_2S donor (AP39) provides renal protection against I/R injury by downregulating the production of proinflammatory markers (IL-12) and scavenging the free radicals, which manifested with a reduction in the nitrogen blood urea and creatinine and improving the histological changes in renal epithelial cells [32]. Systemic administration of NaHS before or after ischemic insult limits I/R injury and provides significant long-term protection [31,33]. NaHS (50 μmol/kg/day) improved regional blood flow in ischemic limb [34]. Therefore, this observation may lead us to observe the effect of NaHS on the experimental animal model of acute tubular necrosis and to extend the research to humans if the results obtained are promising.

Diabetic nephropathy

In experimental animal models of diabetes, H_2S reduced the renal injury from glycation [35]. Its effects on the renal tissue included the glomeruli and the tubular system, leading to increased renal blood flow, glomerular filtration rate, and urinary sodium excretion [36]. H_2S *per se* inhibits the synthesis of protein in renal epithelial cells induced by hyperglycemia [35]. In an experimental diabetic animal model study that used streptozotocin in rats, NaHS significantly reduced the levels of blood pressure, serum glucose, creatinine, and blood nitrogen urea, as well as had favorable effects against oxidative and nitrative stress syndromes [37]. Moreover, in this animal model of diabetes, NaHS acts in a synergism profile with losartan in reducing the blood pressure and serum creatinine [37]. S-propargyl-cysteine, a novel H_2S-releasing compound, protects the kidney from streptozotocin-induced diabetes mellitus by suppressing the expression of mRNA of fibronectin and type IV collagen, inhibiting mesengial cell proliferation and hypertrophy induced by high glucose, and attenuating the inflammatory process that accompanies diabetic kidneys [38]. In one clinical trial that included 1004 type-2 diabetic patients, it has been found that excess urinary secretion of sulfate (a metabolite of H_2S) is associated with a decline in renal risk markers, including microalbuminuria and serum creatinine level [39]. Moreover, chronic hemodialyzed patients due to diabetic nephropathy have low plasma levels of H_2S compared with those without diabetic nephropathy, and it is positively correlated with high-sensitivity C reactive protein and TNF-1β, indicating that the H_2S molecule is involved in the signaling of abnormalities that occurred in diabetic nephropathy [40]. It is important to mention here that the production of H_2S occurred in the β-cell of pancreas and its synthesis is mediated by cystathionine γ-lyase and cystathionine β-synthase, and hyperglycemia induced an increased production of H_2S through cystathionine γ-lyase only [41,42]. Multiple mechanisms are involved in renal protection offered by H_2S at the kidney level rather than at the pancreas because it is well known that H_2S induced cytotoxic effect upon β-pancreatic cells and caused diabetes mellitus [43].

In diabetes mellitus, H_2S donors showed a wide spectrum of beneficial effects and thereby may protect the kidney from diabetic complications. The evidence on the beneficial effects of H_2S donors included the following.

(1) The synthesis of H_2S declines as the complications of diabetes increases. Using H_2S donors may be highly successful in obviating these complications [44,45].
(2) Plasma H_2S levels are reduced in overweight and obese patients, a feature of metabolic syndrome and commonly observed in type-2 diabetes [46].
(3) H_2S or its donors have an antiatherogenic property and act by inhibiting the oxidation of LDL as a result of scavenging the free radicals (notably hypochlorus acid and hydrogen peroxide), inhibition of the myeloperoxidase enzyme, and inhibition of the foam cell formation by several mechanisms [47,48].

Analgesic nephropathy

Administration of H_2S donors to patients treated with NSAIDs and patients who presented with analgesic nephropathy is potentially of great benefit for the following reasons.

(1) A significant decrease in endogenous H_2S enzymatic production was observed using indomethacin, aspirin, diclofenac, and ketoprofen [49]. Therefore, it is reasonable to expect that H_2S donors are effective in preventing NSAID-induced renal damage. Previous studies showed that NaHS and diallyl disulfide protect the gastric mucosa from injury caused by NSAIDs [19,49].
(2) H_2S-releasing NSAID derivatives are synthesized by conjugating a molecule of an NSAID with one H_2S donor. An example of these compounds is S-diclofenac, which has a low gastrointestinal toxicity compared with diclofenac and protects the targets from I/R injury in animals [50]. S-Diclofenac significantly increases the tissue levels of glutathione and inhibits the production of NF-κβ and TNF-α in addition to its inhibitory effects upon angiogenesis and cell proliferation.
(3) Moreover, H_2S-releasing NSAID derivatives have superior anti-inflammatory and analgesic properties compared with parent NSAID [51].

Homocysteinemia

High plasma levels of homocysteine were reported in patients with chronic kidney disease or those managed with hemodialysis and is involved in a further renovascular injury because homocysteine increases blood pressure as a result of inducing arteriolar constriction and stiffness, endothelial damage, and increased sodium absorption [52–55]. H_2S protects the kidney and alleviates renal damage by upregulating the vascular endothelial growth factor, attenuating the production of the extracellular matrix proteins, and decreasing the expression of inflammatory cytokines [25,56]. Its effect

extended to ameliorate the renal function in chronic renal failure that resulted from homocysteinemia [57].

Experimental obstructive nephropathy

Kidney fibrosis is the late sequel of ureter obstruction and it is accompanied by inhibition of the enzyme activity involved in the synthesis of endogenous H_2S. Jung *et al.* [58] reported in experimental studies that using NaHS attenuated the low renal levels of endogenous H_2S and improves the renal antioxidant activities.

H_2S donors (NaHS) suppressed the oxidative stress by preserving catalases such as Cu-Zn-SOD and Mn-SOD, and glutathione levels [59]. H_2S-releasing hybrid sildenafil may be potentially useful in the management of benign prostatic hypertrophy. In one study, it was observed that sildenafil relaxed the urinary bladder by increasing the production of H_2S as a result of activation cystathionine β-synthase and cystathionine γ-lyase enzymes, which are available in the urinary bladder dome [59].

Renal transplantation

Snijder *et al.* [60] pointed out that H_2S interacts with NO and carbon monoxide in renal transplantation and exerts cytoprotection and reduction in tissue injury in the transplanted organ. H_2S protects the donor kidneys against cold I/R injury. In experimental animal models of kidney transplantation, NaHS improves the survival and the function of the early allograft and minimizes cell necrosis, but it does not affect allograft rejection [61].

Anemia of chronic renal failure

Anemia due to chronic renal failure resulted from low renal production of erythropoietin. Experimental studies demonstrated that H_2S donors activate the cellular production of erythropoietin hormone under hypoxia [62]. Therefore, these compounds may be useful medicines in the treatment of anemia that complicated chronic renal failure.

Renal cancer

H_2S is proangiogenic and cytoprotective transmitter against cell cancer. Sonke *et al.* [63] found that endogenous H_2S levels were high clear cell renal cell carcinoma characterized by Von Hippel–Lindau deficiency, and systemic inhibition of endogenous H_2S production reduced the vascularization of Von Hippel–Lindau-deficient clear cell renal cell carcinoma xenografts. H_2S promotes cancer cell death and inhibits cancer angiogenesis and metastasis through its effects on the signaling pathway such as the mitogen-activated protein kinase pathway. In addition, H_2S plays a role in the regulation of the cell cycle and microRNAs, and the metabolism of cancer cells [64].

Discussion

In this review, the endogenous H_2S as a gasotransmitter as well as the exogenous H_2S of different pharmaceutical preparations offered promising effects on kidney diseases because this transmitter acts on the glomeruli and the transport system. Although the renoprotection of H_2S is attributed to the different mechanisms, the exact effect is still unknown [36]. Its protection was observed not only in the kidney but also in other organs, particularly whenever there is evidence of atherosclerosis, endothelial dysfunction, inflammation, and oxidative stress syndrome [65]. H_2S-releasing NSAIDs to protect gastrointestinal mucosa and to enhance the activity of these compounds were investigated and showed promising results [66]. As the discovery of these compounds is still in the infancy, it is expected that H_2S-releasing selective NSAIDs are still not investigated. H_2S-releasing compounds, as mentioned in Tables 1 and 2, are also extended to include other substances (e.g. natural compounds such as garlic or synthetic drugs such as sildenafil, and mesalamine) [67]. Literature survey does not reveal any evidence of Food and Drug Administration approval of these compounds; this may be due to conflicting publishing results – that is, dual effect [68].

Conclusion

H_2S donors provide a broad spectrum of biological activities and protect the renal tissues against a wide variety of primary or secondary renal disorders. A suitable pharmaceutical preparation is necessary to be launched in the markets for the prevention and treatment of acute/chronic renal diseases.

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Conflicts of interest

There are no conflicts of interest.

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