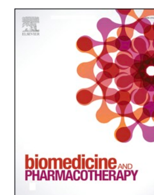
Biomedicine & Pharmacotherapy 166 (2023) 115396

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Physiological role of hydrogen sulfide in the kidney and its therapeutic implications for kidney diseases

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ARTICLE INFO

Keywords:
Hydrogen sulfide (H_2S)
Sodium-potassium-ATPase (Na^+/K^+-ATPase)
Sodium-potassium-chloride (Na^+-K^+-$2Cl^-$) cotransporter
Renal blood flow (RBF)
Glomerular filtration rate (GFR)
H_2S-producing enzymes

ABSTRACT

For over three centuries, hydrogen sulfide (H_2S) has been known as a toxic and deadly gas at high concentrations, with a distinctive smell of rotten eggs. However, studies over the past two decades have shown that H_2S has risen above its historically notorious label and has now received significant scientific attention as an endogenously produced gaseous signaling molecule that participates in cellular homeostasis and influences a myriad of physiological and pathological processes at low concentrations. Its endogenous production is enzymatically regulated, and when dysregulated, contributes to pathogenesis of renal diseases. In addition, exogenous H_2S administration has been reported to exhibit important therapeutic characteristics that target multiple molecular pathways in common renal pathologies in which reduced levels of renal and plasma H_2S were observed. This review highlights functional anatomy of the kidney and renal production of H_2S. The review also discusses current understanding of H_2S in renal physiology and seeks to lay the foundation as a new targeted therapeutic agent for renal pathologies such as hypertensive nephropathy, diabetic kidney disease and water balance disorders.

1. Introduction

Hydrogen sulfide (H_2S) is a colorless, flammable, membrane-permeable and foul-smelling gas that was first described by Bernardino Ramazzini in 1713 as a toxic gas and subsequently established in the toxicological literature as a fatal gas at high concentrations [1–4]. However, experimental evidence over the past two decades has established a rapid paradigm shift in which H_2S functions as an endogenous signaling molecule that participates in cellular homeostasis and influences a myriad of physiological and pathological processes at low concentrations [5–8]. In addition, low physiological concentrations of H_2S produce pharmacological effects, affirming the fact that H_2S has successfully overcome its historic notorious label in the toxicological literature. For example, several studies have shown that H_2S exhibits antioxidant and anti-inflammatory effects at low concentrations as opposed to pro-oxidant and pro-inflammatory effects at high concentrations [9–12]. Also, low H_2S concentrations stimulates cellular respiration whereas inhibitory effect on cytochrome *c* oxidase at high concentrations has been well-documented [13–16]. Thus, H_2S exerts cytoprotection at low concentrations in contrast to cytotoxicity at high concentrations.

H_2S is now established among researchers as the third identified member of a family of gaseous signaling molecules (gasotransmitters) after nitric oxide and carbon monoxide [17–19]. In mammalian cells, H_2S is enzymatically produced at low physiological and non-toxic concentrations using the sulfur-containing amino acid, L-cysteine as a substrate, and catalyzed by the cytosolic enzymes, cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CSE) [20] and the mitochondrial enzyme, 3-mercaptopyruvate sulfurtransferase (3-MST) [21]. Interestingly, a fourth enzymatic pathway involving the peroxisomal enzyme, D-amino acid oxidase (DAO) coupled with 3-MST, also produces H_2S from D-cysteine, a naturally occurring enantiomer of L-cysteine [22] (Fig. 1).

2. Effects of hydrogen sulfide on renal physiology

2.1. Functional anatomy of the kidney

The kidney is a complex organ and crucial to survival. As a pair, they are highly vascularized, receiving about 25% of the total cardiac output.

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https://doi.org/10.1016/j.biopha.2023.115396
Received 21 July 2023; Received in revised form 21 August 2023; Accepted 26 August 2023
Available online 28 August 2023
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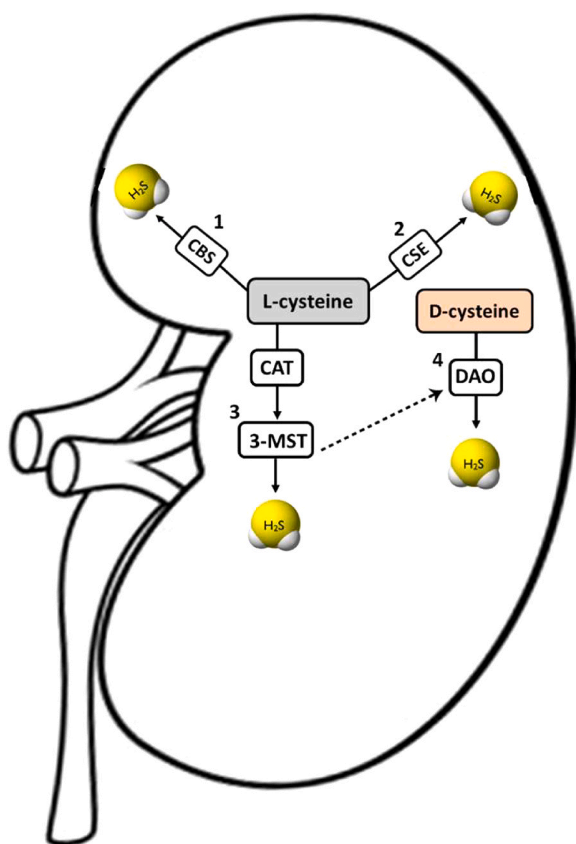

Fig. 1. Simplified view of hydrogen sulfide production in the kidney. (1) H_2S production by CBS using L-cysteine as a substrate; (2) H_2S production by CSE using L-cysteine as a substrate; (3) H_2S production by 3-MST using L-cysteine as a substrate; (4) H_2S production by DAO using D-cysteine as a substrate. H_2S, Hydrogen sulfide; CBS, Cystathionine beta-synthase; CSE, Cystathionine gamma-lyase; CAT, Cysteine aminotransferase; 3-MST, 3-mercaptopyruvate sulfurtransferase; DAO, D-amino acid oxidase.

They filter about 150–200 liters of fluid daily from renal blood flow (RBF). This allows for toxins, metabolic waste products, and excess electrolytes to be excreted while preserving important substances in the blood that are needed by the body. In addition, the kidneys are actively involved in water regulation, a role which is supported by high expression of aquaporins (AQP), integral membrane proteins that serve as water channels. By regulating body fluids and maintaining electrolyte and acid-base balance, the kidneys regulate blood pressure and ensure normal function of other organs [23–25]. The anatomical and functional unit of the kidney is the nephron, which is divided into two portions, namely, the glomerulus (a network of capillary filtration unit) and the tubular system that is responsible for selective reabsorption and secretion in the process of urine production. The tubular system is subdivided into proximal tubule, descending and ascending limbs of loop of Henle, distal tubule, connecting tubule and collecting duct [23–25]. Following filtration by the glomeruli, the filtrate is transported along the regions of the tubular system, where the proximal tubule selectively reabsorbs about two-thirds of the filtered sodium from the filtrate, a process that is regulated by transmembranal sodium-proton (Na^+/H^+) antiporter and sodium-potassium-ATPase (Na^+/K^+-ATPase). Sodium reabsorption also occurs in the ascending limb of the loop of Henle via the action of sodium-potassium-chloride (Na^+-K^+-$2Cl^-$) cotransporter while sodium transport in distal tubule is by the actions of sodium-chloride (Na-Cl) cotransporter, and transport in the connecting tubule and collecting duct is under the control of epithelial sodium channel (ENaC) [23]. It is important to note that the descending limb of the loop of Henle reabsorbs water from the glomerular filtrate as well as in other regions of the tubular system through AQP, except for the thick ascending limb of the loop of Henle and the early distal tubule, which are water-impermeable. Hence, these two regions are known as the diluting segments of the nephron, producing free water (or solute-free water) [23]. Surrounding the renal tubules are peritubular capillaries, which originate from efferent arteriole, and return the bulk of the solutes and water reabsorbed by the tubular system into systemic circulation (i.e. the venous system) and conserved for the body's use. The tubular system is also equipped with secretory pathways that dispose of drugs and metabolites and other unwanted substances such as creatinine, ammonia, urea and uric acid from the peritubular capillaries into the glomerular filtrate and excreted in urine [23]. Thus, the elaborate reabsorption and secretory pathways modify the composition of the glomerular filtrate such that the kidneys produce about 1–2 litres of urine per day.

2.2. *Renal production of hydrogen sulfide*

The distribution of all four H_2S-producing enzymes is subcellular and tissue-specific. In the kidney, however, they are abundantly expressed by endothelial cells, mesangial cells, and podocytes within the glomeruli, as well as in the brush border and cytoplasm of epithelial cells of the renal proximal tubules, distal tubules and in the peritubular capillaries, with CBS and CSE being the most dominant. This makes the kidney a rich source of endogenous H_2S production compared to other organs. Using marker enzymes of known localization in a study to characterize the renal involvement in homocysteine metabolism, both CBS and CSE were reported to be localized in the proximal tubules of rat kidneys [26]. While CBS was expressed by proximal tubular cells in the outer cortex, CSE was localized in the inner cortex and outer medulla [26]. Subsequent studies corroborated this finding using different methods in mouse and rat kidneys [27–29]. Specifically, both enzymes are expressed in the brush border and cytoplasm of epithelial cells of the renal proximal tubules, distal tubules and in the peritubular capillaries [22,30–34]. In addition to the tubular localization of CBS and CSE, we also found both enzymes in the glomeruli of rats subjected to hypothermic injury and diabetic nephropathy [35,36]. However, CSE is the main H_2S-producing enzyme in the glomeruli, which is expressed by endothelial cells, mesangial cells and podocytes [32–34]. Besides animal kidneys, CSE was also found to be expressed in the glomerular and tubulointerstitial compartments of human kidneys [34]. Unlike CBS and CSE, which are the main H_2S-synthesizing enzymes in the kidney, 3-MST and DAO have been less studied and their significance in mediating H_2S-generating pathways have so far received little scientific attention. Nevertheless, they are also expressed in the kidney [22,37,38], with 3-MST specifically found in epithelial cells of the proximal tubule [38]. In total, about 75% of all renal cells and 87% of endothelial cells express H_2S-producing enzymes [32,34], making the kidney a rich source of endogenous H_2S production and with important roles in renal function. This explains why all the known pathways of H_2S production have been described in the kidney. Interestingly, deficiency in H_2S-synthesizing enzymes and significantly reduced plasma H_2S levels have recently been reported in human patients and experimental animals, which correlated with severity of kidney diseases [39–42]. These findings imply that H_2S restoration could be a therapeutic target in human kidney diseases. Fig. 1 is a simplified illustration of endogenous H_2S production in the kidney. It is important to note that besides its endogenous production, H_2S can also be administered exogenously by inhalation or via H_2S donor compounds to augment endogenous H_2S level. These H_2S donor compounds include sodium hydrosulfide (NaHS), sodium sulfide (Na_2S), sodium thiosulfate, GYY4137, AP39, AP123, SG1002, S-propargyl cysteine (SPRC; also known as ZYZ-802), sulfurous mineral water and garlic-derived polysulfide [8,43–47].

2.3. Hydrogen Sulfide Involvement in Renal Function

Several lines of empirical evidence have established the involvement of H_2S in the regulation of cellular physiology via a wide array of mechanisms such as regulation of kinases, ion channels and transcription factors through post-translational S-sulfhydration of cysteine residues. H_2S also binds to heme in heme-containing proteins, as well as functioning as a free radical scavenger and a donor of electrons to the mitochondrial electron transport chain to increase mitochondrial ATP production and regulate bioenergetics [48–51]. In the kidney, H_2S functions to regulate many physiological processes including renal blood flow, glomerular filtration rate, diuresis, natriuresis kaliuresis, and blood pressure. In addition, H_2S also functions as an oxygen sensor in the renal medulla to ensure oxygen balance and improve medullary blood flow. H_2S also modulates renin-angiotensin-aldosterone system to regulate blood volume, blood pressure and renal hemodynamics.

2.3.1. Effect of hydrogen sulfide on renal excretory function

In the kidney, H_2S has been shown to alter cellular function in a variety of ways which result in diverse downstream effects. In a porcine model of kidney transplantation, for example, infusion of Na_2S (an H_2S donor) 10 min before and 20 min after reperfusion of cold-stored porcine kidneys reversed cyclosporine-induced vasoconstriction and other pathological changes through increased renal blood flow (RBF) and glomerular filtration rate (GFR; an index of renal clearance function) [52]. Similarly, in a genetic model of hyperhomocysteinemia (a risk factor in chronic kidney disease progression), heterozygous CBS mice ($CBS^{+/-}$) showed a reduced GFR, which was associated with elevated systolic blood pressure and renal dysfunction while GFR was restored, and renal protection observed in $CBS^{+/-}$ mice which received H_2S-suppemented drinking water (30 μM NaHS for 8 weeks) [53]. Also, in a study to determine the effect of H_2S on renal hemodynamics and function in rats, intrarenal arterial infusion of NaHS (another H_2S donor) at a rate of 50 μL/min increased RBF and GFR, and also promoted natriuresis and kaliuresis, which correlated positively with increased plasma H_2S level, renal CBS and CSE expression [54]. In addition, pharmacological inhibition of endogenous H_2S with aminooxyacetic acid (AOAA; CBS inhibitor) and propargylglycine (PAG; CSE inhibitor) together reduced RBF and GFR, resulting in increased Na^+ and K^+ reabsorption [54–56]. It is worth noting that failure of the kidney to remove excess Na^+, for example, is associated with detrimental pathological effects, due to its role in regulating blood volume, fluid balance and blood pressure. In a recent clinical study involving 157 non-dialysis patients with chronic kidney disease (CKD), Kung and colleagues [57] reported that plasma H_2S and mRNA levels of CBS and CSE in blood mononuclear cells of these patients were significantly lower compared to healthy controls, which corresponded with reduced GFR and severity of the disease. However, mRNA level of 3-MST was markedly increased in the CKD patients [57], suggesting a compensatory effect between the H_2S-producing enzymes.

Mechanistically, the increased RBF and GFR by H_2S suggests a vasodilatory effect on afferent arterioles by reducing renal vascular resistance possibly via activation of K_{ATP} channels (the main vascular target of H_2S), as pharmacological blockade of K_{ATP} channels with 10 μM glibenclamide during renal ischemia-reperfusion injury potentiated further injury on renal epithelial integrity in a rat model of isolated perfused kidney [58]. Also, H_2S activates NO/cGMP/sGC/PKG pathway [59,60], one of the most extensively studied vasodilatory pathways, which altogether, could account for the increased RBF and GFR in the above studies. This also suggests that H_2S interacts with other members of the gasotransmitter family to induce vasodilation. In the case of increased natriuresis and kaliuresis, H_2S administration through NaHS inhibited the activities of Na^+/K^+-ATPase and Na^+-K^+-$2Cl^-$ cotransporter in the renal tubules [54,56], thereby preventing the reabsorption of these ions and potentiating their excretion (Fig. 2). In a greater detail, the inhibitory effect of H_2S on Na^+/K^+-ATPase has been shown to be due to its ability to directly target H_2S-sensitive disulfide bonds in epidermal growth factor receptor (EGFR) in the proximal tubule, resulting in endocytosis and inhibition of Na^+/K^+-ATPase via EGFR/GAB1/PI3-K/Akt signaling pathway [56]. In addition, exogenous H_2S administration prevents hydrogen peroxide-induced activation and opening of ENaC in the distal tubule via phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) pathway [61], and thereby reducing Na^+ reabsorption and increasing its excretion. There are studies also showing increased activity of Cl^-/HCO_3^- exchanger in aortic tissues of rats as well in vascular smooth muscle cells [62,63]. Although this has not been studied in the kidney, it is possible that H_2S exhibits the same effect in renal tissues considering the crucial role of Cl^-/HCO_3 exchanger in regulating ion excretion and maintaining physiological pH. Taken together, H_2S increases RBF, GFR and excretory function of the kidney by inhibiting the activities of transporters such as Na^+-K^+-$2Cl^-$ and Na^+/K^+-ATPase.

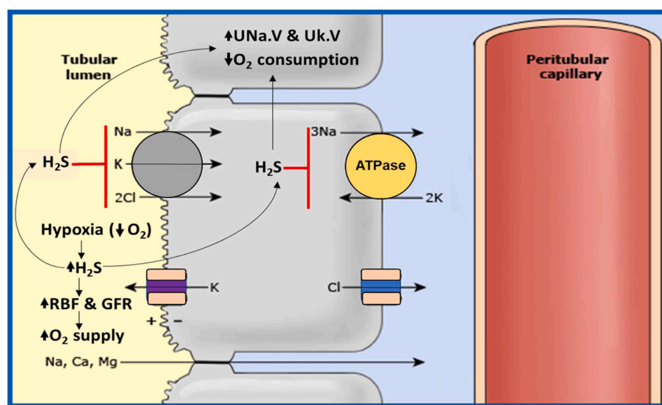

Fig. 2. Effects of H_2S on renal function. H_2S induces vasodilation and also blocks renal tubular transport by inhibiting the activities of Na^+/K^+-ATPase and Na^+-K^+-$2Cl^-$ cotransporter, and thereby increasing RBF and GFR, and promoting natriuresis (UNa.V) and kaliuresis (Uk.V). H_2S also functions as an oxygen sensor under hypoxic condition in the renal medulla in which its production increases, leading to oxygen restoration and further enhancing RBF and GFR as well as suppressing tubular transport. H_2S, hydrogen sulfide; RBF, renal blood flow; GFR, glomerular filtration rate; UNa.V, urinary sodium, Uk.V; urinary potassium.

2.3.2. Role of hydrogen sulfide in renal water handling

As mentioned in Section 2.1, aquaporins (AQPs), also known as water channels, are a family of transmembrane proteins that regulate intracellular and intercellular water flow by mediating bi-directional flow of water and small uncharged solutes such as glycerol, urea, ammonia, and hydrogen peroxide down an osmotic gradient, and thus influencing the overall process of urine concentration [64]. AQPs are widely expressed in specific cell types in various tissues. In the kidney, there are 9 AQPs distributed at various regions of the nephron. They are AQP1, AQP2, AQP3, AQP4, AQP5, AQP6, AQP7, AQP8 and AQP11 [64,108]. AQP1 is a highly selective water-permeable channel localized in apical and basolateral membrane of the epithelial cells of the proximal tubules, thin descending limb of loop of Henle and descending vasa recta [65] while AQP2 is highly concentrated in the apical membrane of collecting duct principal cells (epithelial cells) and involved in regulating urine concentration [66]. AQP3 and AQP4 are found in the basolateral cell membrane of principal collecting duct cells, exporting water in the cytoplasm [67,68]. AQP5 and AQP6 are localized in intercalated cells of the collecting duct. However, their functions are not completely understood [69,70]. AQP 7 is localized in the brush border of the S3 segment (straight portion) of the proximal tubule and regulates glycerol transport, where it mediates glycerol and water transport [71], whereas AQP8 is found in the epithelial cells of proximal tubule, principal cells of collecting duct and mitochondrial membrane, where it regulates ammonia transport [108]. AQP11 is expressed in the

endoplasmic reticulum of epithelial cells of the proximal tubules and plays a crucial role in water and glucose reabsorption [72]. Among the renal AQPs, AQP2 is the major regulator of urine concentration, whose function is regulated by arginine vasopressin via activation of intracellular cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling pathway [73,74]. In addition, cAMP response element-binding protein (CREB), a ubiquitously expressed nuclear transcription factor, has been reported to enhance transcription from AQP2 promoter through cAMP response element [75,76]. It is important to mention that PKA phosphorylates AQP2 in addition to other kinases that regulate localization of AQP2, and thereby facilitating AQP2 accumulation on the plasma membrane [109]. Interestingly, alteration in AQP2 protein expression is associated with water balance disorders such as nephrogenic diabetes insipidus, nephrogenic syndrome of inappropriate antidiuresis, syndrome of inappropriate antidiuretic hormone secretion, and autosomal dominant polycystic kidney disease [77–79]. This finding suggests that vasopressin-AQP2 pathway could be a therapeutic target in the treatment and/or pharmacological management of water balance disorders, and that urinary AQP2 could serve as a useful biomarker for diagnosis of these disorders.

Burgeoning preclinical evidence shows that H_2S upregulates renal AQP2 expression via cAMP/PKA signaling pathway, and thereby improving urine concentration in water balance disorders (Fig. 3). In a mouse model of lithium-induced nephrogenic diabetes insipidus (NDI), a rare water balance disorder characterized by polyuria and polydipsia, Luo et al. [79] reported that coadministration of the endogenous H_2S inhibitors, AOAA (10 mg/kg/d; against CBS) and PAG (30 mg/kg/d; against CSE) for 5 days, was associated with a 40% decrease in AQP2 protein expression in the inner medullary collecting duct along with significant downregulation in the expression of renal phosphorylated CREB (p-CREB) protein compared to control mice. This observation aligned with marked downregulation of renal AQP2 mRNA expression and a 70% reduction in endogenous H_2S production in the renal inner medulla. Similar results were obtained in the renal cortex. In a separate experiment by the same authors, AOAA and PAG coadministration in dehydrated mice exhibited a 20% decrease in urine osmolality and 25% increase in urine production compared to dehydrated control mice. This corresponded with significant downregulation in AQP2 and p-CREB protein expression in the renal inner medulla [79], and suggests a urine concentration defect following endogenous H_2S inhibition. However, intraperitoneal administration of the H_2S donor, GYY4137 (50 mg/kg/d) for 7 days markedly upregulated AQP2 protein expression in the renal inner medulla of lithium-induced (NDI) mice compared to NDI control mice. As expected, this was consistent with increased urine osmolality and significantly improved urine concentration [79]. Using an in vitro model, treatment of primary cultured inner medullary collecting duct cells of rats with NaHS and GYY4137 resulted in increased AQP2 protein expression after 5 min of treatment, and was associated with increased cAMP level in the cell lysate. However, this effect was significantly abrogated with the PKA inhibitor, H89 or adenylyl cyclase in rat inner medullary collecting duct suspensions [79]. This result further affirms the observation that increased renal AQP2 expression and improvement in urine concentration by H_2S is via cAMP/PKA signaling pathway (Fig. 3). As H_2S is an activator cAMP/PKA pathway under NDI condition, it is important to note that H_2S also activates cAMP/PKA signaling pathway in different cell types under different conditions [80]. Overall, despite this promising experimental result, the finding is from only one study, which makes clinical translation difficult. Therefore, more studies from other research groups with the same and other H_2S donors and at different doses are required to corroborate this result. However, it can be concluded from this single study that H_2S treatment could represent a novel therapy that targets vasopressin-AQP2 pathway in water balance disorders such as NDI.

2.3.3. Role of hydrogen sulfide as an oxygen sensor in renal function

As mentioned in Section 2.1 above, the kidney receives about 25% of the total cardiac output. However, the medullary compartment receives only about 10% of the total renal perfusion in functionally normal kidney due to intrarenal arteriovenous oxygen shunt [81]. This makes the renal medulla highly vulnerable to pathological conditions. Available evidence indicates that H_2S is an oxygen sensor and mediates tubulovascular cross-talk in the renal medulla [82–87]. While the production of H_2S is independent of oxygen, its oxidative metabolism in mitochondria is oxygen-dependent. Thus, the low oxygen partial pressure in the renal medulla creates a hypoxic environment that leads to H_2S accumulation, which increases the activity of H_2S including electron donation for ATP production in the mitochondria, and restoration of oxygen balance by increasing medullary flow and decreasing tubular Na^+ transport, which accounts for 60% of renal oxygen consumption [55,82–87] (Fig. 2). Considering that majority of Na^+-K^+-$2Cl^-$ channels are found in thick ascending limb of the loop of Henle, which also expresses CBS, and requires a balance between oxygen supply and hyperosmolality for urine concentration [28], the finding that H_2S functions as an oxygen sensor in the renal medulla is very important. The oxygen-sensing ability of H_2S is also supported by the fact that CBS and CSE translocate into mitochondria under hypoxic conditions to increase endogenous H_2S production along with 3-MST [13,88]. Besides the kidney, H_2S-mediating oxygen sensing has also been reported in the

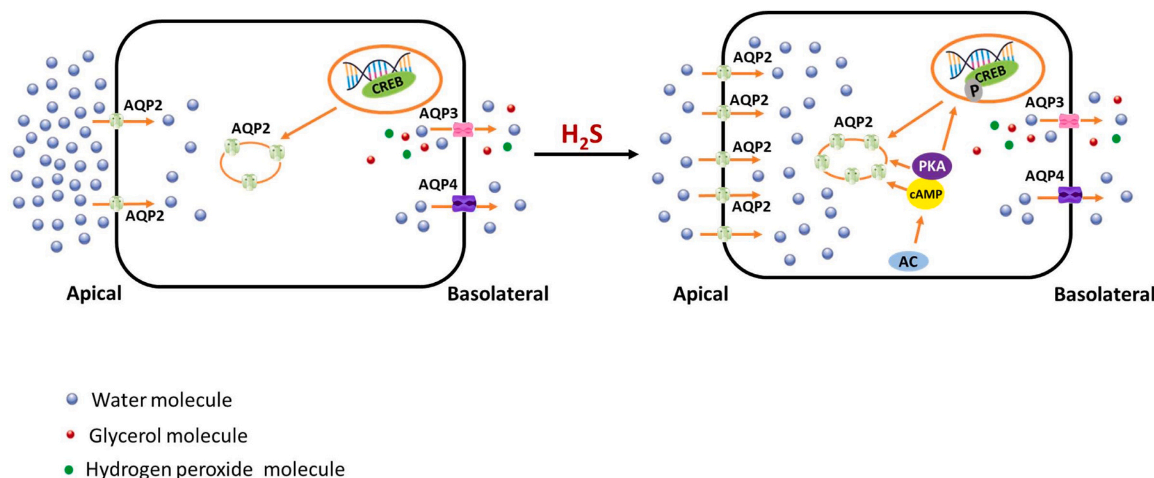

Fig. 3. Role of H_2S in renal water handling. H_2S activates intracellular cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling pathway, and thereby upregulating renal aquaporin 2 (AQP2) expression. This decreases urine osmolality and improves urine concentration in water balance disorders such as nephrogenic diabetes insipidus.

heart, lungs and gastrointestinal tract, thus affecting blood flow and regulating oxygen balance in these tissues [89–91]. However, the specific mechanisms and downstream signaling events require further investigations. In summary, H_2S functions as an oxygen sensor under hypoxic conditions, and thereby increasing medullary flow, inhibiting tubular transport and restoring oxygen balance.

2.3.4. Effect of hydrogen sulfide on intrarenal renin release

The renal-angiotensin-aldosterone system (RAAS) is a critical renovascular humoral regulatory system in the body that is composed of hormones, enzymes, proteins and a series of reactions that regulate blood volume, blood pressure, renal hemodynamics and systemic vascular resistance by regulating water, plasma sodium (salt) excretion and vascular tone on a long-term basis through coordinated effects on the heart, blood vessels and kidneys [92,93]. As a compensatory protective mechanism, the RAAS is activated by a pressure transducer mechanism involving mechanoreceptors in afferent arterioles in response to conditions such as renal hypoperfusion and hypotension (such as during hemorrhage or dehydration) in the early stages of cardiovascular and renal diseases [92,93]. The RAAS is also activated by abnormally low concentration of sodium chloride, which is sensed by macula densa cells in the distal convoluted tubule and generate paracrine signals in the juxtaglomerular cells present within the walls of the afferent arterioles of the kidney to release renin [94,95]. However, chronic activation of RAAS is pathological, as it produces adverse effects such as syndromes of congestive heart failure, systemic hypertension, and chronic kidney disease [96,97]. Thus, RAAS activity is determined and regulated by the release of renin, a process which has been well-documented to be mediated by intracellular cAMP (a second messenger in signal transduction) [98–101].

Administration of H_2S has been found to modulate renin release when RAAS is overactivated (Fig. 4). In a two-kidney-one-clip (2K1C) model of renovascular hypertension in rats, daily intraperitoneal administration of 5.6 mg/kg NaHS resulted in significant reduction in renin activity and levels of angiotensin II (a potent vasoconstrictor in the RAAS), which positively correlated with downregulation of renal renin mRNA and protein expressions as well as blood pressure in 2K1C rats compared to vehicle control rats [102]. The anti-hypertensive effect of

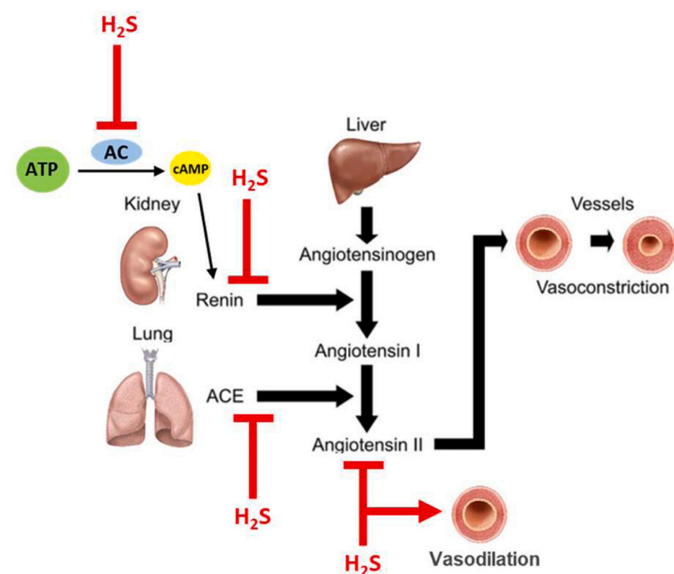

Fig. 4. H_2S modulates renin-angiotensin-aldosterone system (RAAS). Under conditions in which RAAS is overactivated, administration of H_2S inhibits the activities of renin and angiotensin-converting enzyme (ACE) as well as reducing angiotensin II level by suppressing intracellular cyclic adenosine monophosphate (cAMP) production via inhibition of adenylyl cyclase (AC).

H_2S in this study was confirmed by another 2K1C rat model in which daily intraperitoneal administration of 56 μmol/kg of NaHS for 4 weeks inhibited AT_1 receptor activation by angiotensin II, reduced systolic blood pressure and attenuated ventricular dysfunction, resulting in improvement in myocardial remodeling [110]. Using primary cultures of renin-rich kidney cells in a separate experiment, the same authors also reported that treatment with 100 μmol/L of NaHS also significantly suppressed renin activity along with reduction in intracellular cAMP level [102]. This observation was supported by results from later studies in which NaHS (0.1–10 μM) strongly suppressed cAMP production in As4.1 cells (renin-expressing cell line) treated with isoproterenol (a β-adrenoceptor agonist), forskolin (an adenylyl cyclase activator), or 3-isobutyl-1-methylxanthine (a phosphodiesterase inhibitor) by inhibiting the activity of adenylyl cyclase (an enzyme that catalyzes the production of cAMP from ATP), and thus regulating renin activity and blood pressure [103,104] (Fig. 4). In a model of high-salt-induced hypertension in Dahl salt–sensitive rats, feeding on high-salt diet containing 8% NaHS for 8 weeks inhibited RAAS activation in the rat kidney, reversed pathological remodeling and prevented salt-sensitive hypertension, which corresponded with upregulation in renal CBS mRNA and protein expression, 3-MST mRNA expression and significantly increased renal and serum H_2S levels to near normal levels compared to rats fed with high-salt diet without NaHS supplementation [105]. Interestingly, H_2S had no effect on renin activity in normal rats [102], which suggests that H_2S only inhibits renin release when RAAS is overactivated. Using human umbilical vein endothelial cells (a model system for studying endothelial cell function), Laggner et al. [106] also demonstrated that H_2S directly inhibits the activity of angiotensin-converting enzyme (ACE; a zinc-containing vasoconstricting enzyme in the RAAS) in a dose-dependent manner by interfering with zinc in the active center of ACE (Fig. 4).

In addition to these experimental models of hypertension, the effect of H_2S on RAAS was also reported in experimental diabetic models. Using rat mesangial cells cultured in a medium supplemented with high glucose (25 mM), and streptozotocin-induced diabetic rats, Xue et al. [107] observed that high glucose or hyperglycemia downregulated renal expression of CSE and reduced endogenous H_2S production, which resulted in excessive production of reactive oxygen species (ROS; destructive mediator of cell and tissue injury), overactivation of intrarenal RAAS, and culminated in mesangial cell proliferation and abundant extracellular matrix production. Interestingly, in a separate experiment by the same authors, treatment with the CSE inhibitor propargylglycine, produced effects similar to that of high-glucose treatment [107]. However, treatment with 50 μmol/kg/day of NaHS abrogated the high glucose-induced RAAS activation and excess ROS production in the renal mesangial cells, and reversed the pathological changes associated with overactivation of RAAS, without affecting glycemic status in the diabetic rats [107]. Collectively, these empirical findings accentuate the vasodilatory effect of H_2S in addition to suppressing RAAS under conditions in which RAAS is overactivated.

3. Conclusion

Hydrogen sulfide (H_2S), a foul-smelling gas with historic notoriety, has recently emerged as an endogenous gaseous signaling molecule that plays important roles in cellular homeostasis. The kidney is considered one of the major sources of endogenous H_2S production due to the abundant expression of H_2S-producing enzymes in the glomerular and tubular compartments, and thereby influencing normal renal function such as regulation of renal blood flow, glomerular filtration rate, tubular transport, blood pressure, renal bioenergetics and RAAS. Thus, the role of H_2S in renal function implies that it could be considered as a new therapeutic target or biomarker for renal pathologies such as hypertensive nephropathy, diabetic kidney disease and water balance disorders.

CRediT authorship contribution statement

Conceptualization: GJD; Literature search and collection: GJD Manuscript writing: GJD; Manuscript review and editing: GJD; Figure preparation: GJD.

Declaration of Competing Interest

None.

References

[1] B. Ramazzini, The Latin text of 1713, rev. with translation and notes by W.C. Wright, University of Chicago Press,, Chicago, IL, 1940, pp. 151–157 (De Morbis Anificum Diatriba).
[2] C.W. Mitchell, S.J. Davenport, Hydrogen sulphide literature, Public Health Rep. 39 (1924) 1–13.
[3] D.S. Gabbay, F. De Roos, J. Perrone, Twenty-foot fall averts fatality from massive hydrogen sulfide exposure, J. Emerg. Med 20 (2) (2001) 141–144.
[4] R.O. Beauchamp Jr, J.S. Bus, J.A. Popp, C.J. Boreiko, D.A. Andjelkovich, A critical review of the literature on hydrogen sulfide toxicity, Crit. Rev. Toxicol. 13 (1) (1984) 25–97.
[5] K. Abe, H. Kimura, The possible role of hydrogen sulfide as an endogenous neuromodulator, J. Neurosci. 16 (1996) 1066–1071.
[6] W. Zhao, J. Zhang, Y. Lu, R. Wang, The vasorelaxant effect of H_2S as a novel endogenous gaseous KATP channel opener, EMBO J. 20 (2001) 6008–6016.
[7] G. Tang, L. Wu, W. Liang, R. Wang, Direct stimulation of K_{ATP} channels by exogenous and endogenous hydrogen sulfide in vascular smooth muscle cells, Mol. Pharm. 68 (2005) 1757–1764.
[8] M.Y. Zhang, G.J. Dugbartey, S. Juriasingani, M. Akbari, W. Liu, A. Haig, P. McLeod, J. Arp, A. Sener, Sodium thiosulfate-supplemented UW solution protects renal grafts against prolonged cold ischemia-reperfusion injury in a murine model of syngeneic kidney transplantation, Biomed. Pharm. 145 (2022), 112435.
[9] Y. Kimura, H. Kimura, Hydrogen sulfide protects neurons from oxidative stress, FASEB J. 18 (2004) 1165–1167.
[10] M. Whiteman, J.S. Armstrong, S.H. Chu, S. Jia-Ling, B.S. Wong, N.S. Cheung, et al., The novel neuromodulator hydrogen sulfide: an endogenous peroxynitrite 'scavenger'? J. Neurochem 90 (2004) 765–768.
[11] Y. Kimura, Y. Goto, H. Kimura, Hydrogen sulfide increases glutathione production and suppresses oxidative stress in mitochondria, Antioxid. Redox Signal 12 (2010) 1–13.
[12] L. Li, M. Bhatia, Y.Z. Zhu, Y.C. Zhu, R.D. Ramnath, Z.J. Wang, et al., Hydrogen sulfide is a novel mediator of lipopolysaccharide-induced inflammation in the mouse, FASEB J. 19 (2005) 1196–1198.
[13] M. Fu, W. Zhang, L. Wu, G. Yang, H. Li, R. Wang, Hydrogen sulfide (H2S) metabolism in mitochondria and its regulatory role in energy production, Proc. Natl. Acad. Sci. USA 109 (2012) 2943–2948.
[14] M. Goubern, M. Andriamihaja, T. Nübel, F. Blachier, F. Bouillaud, Sulfide, the first inorganic substrate for human cells, FASEB J. 21 (2007) 1699–1706.
[15] C. Szabo, C. Coletta, C. Chao, K. Módis, B. Szczesny, A. Papapetropoulos, et al., Tumor-derived hydrogen sulfide, produced by cystathionine-β-synthase, stimulates bioenergetics, cell proliferation, and angiogenesis in colon cancer, Proc. Natl. Acad. Sci. USA 110 (2013) 12474–12479.
[16] K. Módis, C. Coletta, K. Erdélyi, A. Papapetropoulos, C. Szabo, Intramitochondrial H_2S production by 3-mercaptopyruvate sulfurtransferase maintains mitochondrial electron flow and supports cellular bioenergetics, FASEB J. 27 (2013) 601–611.
[17] P.J. Yates, S.A. Hosgood, M.L. Nicholson, A biphasic response to nitric oxide donation in an ex vivo model of donation after cardiac death renal transplantation, J. Surg. Res 175 (2) (2012) 316–321.
[18] G.J. Dugbartey, K.K. Alornyo, P.P.W. Luke, A. Sener, Application of carbon monoxide in kidney and heart transplantation: A novel pharmacological strategy for a broader use of suboptimal renal and cardiac grafts, Pharm. Res 173 (2021), 105883.
[19] G.J. Dugbartey, Carbon monoxide as an emerging pharmacological tool to improve lung and liver transplantation protocols, Biochem Pharm. 193 (2021), 114752.
[20] R. Hosoki, N. Matsuki, H. Kimura, The possible role of hydrogen sulfide as an endogenous smooth muscle relaxant in synergy with nitric oxide, Biochem Biophys. Res Commun. 237 (1997) 527–531.
[21] N. Shibuya, M. Tanaka, M. Yoshida, Y. Ogasawara, T. Togawa, K. Ishii, H. Kimura, 3-Mercaptopyruvate sulfurtransferease produces hydrogen sulfide and bound sulfane sulfur in the brain, Antioxid. Redox Signal 11 (2009) 703–714.
[22] N. Shibuya, S. Koike, M. Tanaka, M. Ishigami-Yuasa, Y. Kimura, Y. Ogasawara, K. Fukui, N. Nagahara, H. Kimura, A novel pathway for the production of hydrogen sulfide from D-cysteine in mammalian cells, Nat. Commun. 4 (2013) 1366.
[23] D.C. Eaton, J.P. Pooler. Vanders Renal Physiology, ninth ed., McGraw Hill Publisher, 2018.
[24] G. Giebisch, E. Windhanger, Glomerular filtration and renal blood flow, in: W. F. Boron, E.L. Boulpaep (Eds.), Medical Physiology: A Cellular and Molecular Approach, Saunders, Philadelphia, 2009, pp. 767–781.
[25] A. Bhaskar, V. Oommen, A simple model for demonstrating the factors affecting glomerular filtration rate, Adv. Physiol. Educ. 42 (2) (2018) 380–382. Jun 01.
[26] J.D. House, M.E. Brosnan, J.T. Brosnan, Characterization of homocysteine metabolism in the rat kidney, Biochem J. 328 (Pt 1) (1997) 287–292. Pt 1.
[27] I. Ishii, N. Akahoshi, X.N. Yu, Y. Kobayashi, K. Namekata, G. Komaki, H. Kimura, Murine cystathionine gamma-lyase: complete cDNA and genomic sequences, promoter activity, tissue distribution and developmental expression, Biochem. J. 381 (Pt 1) (2004) 113–123.
[28] N. Li, L. Chen, R.W. Muh, P.L. Li, Hyperhomocysteinemia associated with decreased renal transsulfuration activity in Dahl S rats, Hypertension 47 (2006) 1094–1100.
[29] P. Tripatara, N.S. Patel, V. Brancaleone, D. Renshaw, J. Rocha, B. Sepodes, H. Mota-Filipe, M. Perretti, C. Thiemermann, Characterisation of cystathionine gamma-lyase/hydrogen sulphide pathway in ischaemia/reperfusion injury of the mouse kidney: an in vivo study, Eur. J. Pharm. 606 (1–3) (2009) 205–209.
[30] J. Yamamoto, W. Sato, T. Kosugi, T. Yamamoto, T. Kimura, S. Taniguchi, et al., Distribution of hydrogen sulfide (H_2S)-producing enzymes and the roles of the H_2S donor sodium hydrosulfide in diabetic nephropathy, Clin. Exp. Nephrol. 17 (1) (2013) 32–40.
[31] M. Xia, L. Chen, R.W. Muh, P.L. Li, N. Li, Production and actions of hydrogen sulfide, a novel gaseous bioactive substance, in the kidneys, J. Pharm. Exp. Ther. 329 (3) (2009) 1056–1062.
[32] H.J. Lee, M.M. Mariappan, D. Feliers, R.C. Cavaglieri, K. Sataranatarajan, H. E. Abboud, et al., Hydrogen sulfide inhibits high glucose-induced matrix protein synthesis by activating AMP-activated protein kinase in renal epithelial cells, J. Biol. Chem. 387 (7) (2012) 4451–4461.
[33] E.M. Bos, H.G. Leuvinink, P.M. Snijder, et al., Hydrogen sulfide-induced hypometabolism prevents renal ischemia/reperfusion injury, Am. J. Soc. Nephrol. 20 (9) (2009) 1901–1905.
[34] E.M. Bos, R. Wang, P.M. Snijder, et al., Cystathionine γ-lyase protects against renal ischemia/reperfusion by modulating oxidative stress, Am. J. Soc. Nephrol. 24 (5) (2013) 759–770.
[35] G.J. Dugbartey, F. Talaei, M.C. Houwertjes, M. Goris, A.H. Epema, H.R. Bouma, R.H. Henning, Dopamine treatment attenuates acute kidney injury in a rat model of deep hypothermia and rewarming - The role of renal H_2S-producing enzymes, Eur. J. Pharm. 769 (2015) 225–233.
[36] G.J. Dugbartey, K.K. Alornyo, D.E. Diaba, I. Adams, Activation of renal CSE/H_2S pathway by alpha-lipoic acid protects against histological and functional changes in the diabetic kidney, Biomed. Pharm. 153 (2022), 113386.
[37] M.A. Aminzadeh, N.D. Vaziri, Downregulation of the renal and hepatic hydrogen sulfide (H2S)-producing enzymes and capacity in chronic kidney disease, Nephrol. Dial. Transpl. 27 (2) (2012) 498–504.
[38] N. Nagahara, T. Ito, H. Kitamura, T. Nishino, Tissue and subcellular distribution of mercaptopyruvate sulfurtransferase in the rat: confocal laser fluorescence and immunoelectron microscopic studies combined with biochemical analysis, Histochem Cell Biol. 110 (3) (1998) 243–250.
[39] V. Brancaleone, F. Roviezzo, V. Vellecco, L. De Gruttola, M. Bucci, G. Cirino, Biosynthesis of H2S is impaired in non-obese diabetic (NOD) mice, Br. J. Pharm. 155 (5) (2008) 673–680.
[40] S.K. Jain, R. Bull, J.L. Rains, P.F. Bass, S.N. Levine, S. Reddy, R. McVie, J. A. Bocchini, Low levels of hydrogen sulfide in the blood of diabetes patients and streptozotocin-treated rats causes vascular inflammation? Antioxid. Redox Signal 12 (11) (2010) 1333–1337.
[41] M. Dutta, U.K. Biswas, R. Chakraborty, P. Banerjee, U. Raychaudhuri, A. Kumar, Evaluation of plasma H_2S levels and H_2S synthesis in streptozotocin induced Type-2 diabetes-an experimental study based on Swietenia macrophylla seeds, Asian Pac. J. Trop. Biomed. 4 (1) (2014) S483–S487.
[42] X. Yuan, J. Zhang, F. Xie, W. Tan, S. Wang, L. Huang, L. Tao, Q. Xing, Q. Yuan, Loss of the Protein Cystathionine β-Synthase During Kidney Injury Promotes Renal Tubulointerstitial Fibrosis, Kidney Blood Press Res 42 (3) (2017) 428–443.
[43] E. Ginter, V. Simko, Garlic (Allium sativum L.) and cardiovascular diseases, Bratisl. Lek. Listy 111 (8) (2010) 452–456.
[44] K. Kashfi, K.R. Olson, Biology and therapeutic potential of hydrogen sulfide and hydrogen sulfide-releasing chimeras, Biochem Pharm. 85 (5) (2013) 689–703.
[45] M.M. Safar, R.M. Abdelsalam, H2S donors attenuate diabetic nephropathy in rats: Modulation of oxidant status and polyol pathway, Pharm. Rep. 67 (1) (2015) 17–23.
[46] D. Gerő, R. Torregrossa, A. Perry, A. Waters, S. Le-Trionnaire, J.L. Whatmore, M. Wood, M. Whiteman, The novel mitochondria-targeted hydrogen sulfide (H2S) donors AP123 and AP39 protect against hyperglycemic injury in microvascular endothelial cells in vitro, Pharm. Res. 113 (Pt A) (2016) 186–198.
[47] D.J. Polhemus, Z. Li, C.B. Pattillo, G.Sr Gojon, G.Jr Gojon, T. Giordano, H. Krum, A novel hydrogen sulfide prodrug, SG1002, promotes hydrogen sulfide and nitric oxide bioavailability in heart failure patients, Cardiovasc Ther. 33 (4) (2015) 216–226.
[48] A.K. Mustafa, M.M. Gadalla, N. Sen, S. Kim, W. Mu, S.K. Gazi, R.K. Barrow, G. Yang, R. Wang, S.H. Snyder, H_2S signals through protein S-sulfhydration, Sci. Signal 2 (96) (2009) ra72.
[49] O. Kabil, R. Banerjee, Redox biochemistry of hydrogen sulfide, J. Biol. Chem. 285 (29) (2010) 21903–21907.
[50] Y.H. Liu, C.D. Yan, J.S. Bian, Hydrogen sulfide: a novel signaling molecule in the vascular system, J. Cardiovasc Pharm. 58 (6) (2011) 560–569.

[51] M. Fu, W. Zhang, L. Wu, G. Yang, H. Li, R. Wang, Hydrogen sulfide (H_2S) metabolism in mitochondria and its regulatory role in energy production, Proc. Natl. Acad. Sci. USA 109 (8) (2012) 2943–2948.
[52] G. Lee, S.A. Hosgood, M.S. Patel, M.L. Nicholson, Hydrogen sulphide as a novel therapy to ameliorate cyclosporine nephrotoxicity, J. Surg. Res 197 (2015) 419–426.
[53] S. Pushpakumar, S. Kundu, U. Sen, Hydrogen Sulfide Protects Hyperhomocysteinemia-Induced Renal Damage by Modulation of Caveolin and eNOS Interaction, Sci. Rep. 9 (1) (2019) 2223.
[54] M. Xia, L. Chen, R.W. Muh, P.L. Li, N. Li, Production and actions of hydrogen sulfide, a novel gaseous bioactive substance, in the kidneys, J. Pharm. Exp. Ther. 329 (3) (2009) 1056–1062.
[55] A. Roy, A.H. Khan, M.T. Islam, M.C. Prieto, D.S. Majid, Interdependency of cystathione γ-lyase and cystathione β-synthase in hydrogen sulfide-induced blood pressure regulation in rats, Am. J. Hypertens. 25 (1) (2012) 74–81.
[56] S.N. Ge, M.M. Zhao, D.D. Wu, Y. Chen, Y. Wang, J.H. Zhu, W.J. Cai, Y.Z. Zhu, Y. C. Zhu, Hydrogen sulfide targets EGFR Cys797/Cys798 residues to induce Na(+)/K(+)-ATPase endocytosis and inhibition in renal tubular epithelial cells and increase sodium excretion in chronic salt-loaded rats, Antioxid. Redox Signal 21 (15) (2014) 2061–2082.
[57] Q. Kuang, N. Xue, J. Chen, Z. Shen, X. Cui, Y. Fang, X. Ding, Low Plasma Hydrogen Sulfide Is Associated with Impaired Renal Function and Cardiac Dysfunction, Am. J. Nephrol. 47 (5) (2018) 361–371.
[58] M. Rahgozar, D.A. Willgoss, G.C. Gobé, Z.H. Endre, ATP-dependent K+ channels in renal ischemia reperfusion injury, Ren. Fail 25 (6) (2003) 885–896.
[59] R. Wang, Signaling pathways for the vascular effects of hydrogen sulfide, Curr. Opin. Nephrol. Hypertens. 20 (2011) 107–112.
[60] R. Wang, C. Szabo, F. Ichinose, A. Ahmed, M. Whiteman, A. Papapetropoulos, The role of H_2S bioavailability in endothelial dysfunction, Trends Pharm. Sci. 36 (2015) 568–578.
[61] J. Zhang, S. Chen, H. Liu, B. Zhang, Y. Zhao, K. Ma, D. Zhao, Q. Wang, H. Ma, Z. Zhang, Hydrogen sulfide prevents hydrogen peroxide-induced activation of epithelial sodium channel through a PTEN/PI(3,4,5)P3 dependent pathway, PLoS One 8 (5) (2013), e64304.
[62] Y.H. Liu, J.S. Bian, Bicarbonate-dependent effect of hydrogen sulfide on vascular contractility in rat aortic rings, Am. J. Physiol. Cell Physiol. 299 (4) (2010) C866–C872.
[63] S.W. Lee, Y. Cheng, P.K. Moore, J.S. Bian, Hydrogen sulphide regulates intracellular pH in vascular smooth muscle cells, Biochem Biophys. Res Commun. 358 (4) (2007) 1142–1147.
[64] Y. Li, W. Wang, T. Jiang, B. Yang, Aquaporins in urinary system, Adv. Exp. Med Biol. 969 (2017) 131–148.
[65] C.L. Chou, M.A. Knepper, A.N. Hoek, D. Brown, B. Yang, T. Ma, A.S. Verkman, Reduced water permeability and altered ultrastructure in thin descending limb of Henle in aquaporin-1 null mice, J. Clin. Invest 103 (4) (1999) 491–496.
[66] H. Ren, B. Yang, P.A. Molina, J.M. Sands, J.D. Klein, NSAIDs alter phosphorylated forms of AQP2 in the Inner Medullary Tip, PLoS One 10 (10) (2015), e0141714.
[67] T. Ma, Y. Song, B. Yang, A. Gillespie, E.J. Carlson, C.J. Epstein, A.S. Verkman, Nephrogenic diabetes insipidus in mice lacking aquaporin-3 water channels, Proc. Natl. Acad. Sci. USA 97 (8) (2000) 4386–4391.
[68] Y.H. Kim, J.H. Earm, T. Ma, A.S. Verkman, M.A. Knepper, K.M. Madsen, J. Kim, Aquaporin-4 expression in adult and developing mouse and rat kidney, J. Am. Soc. Nephrol. 12 (9) (2001) 1795–1804.
[69] G. Procino, L. Mastrofrancesco, F. Sallustio, V. Costantino, C. Barbieri, F. Pisani, F.P. Schena, M. Svelto, G. Valenti, AQP5 is expressed in type-B intercalated cells in the collecting duct system of the rat, mouse and human kidney, Cell Physiol. Biochem 28 (4) (2011) 683–692.
[70] D. Promeneur, T.H. Kwon, M. Yasui, G.H. Kim, J. Frøkiaer, M.A. Knepper, P. Agre, S. Nielsen, Regulation of AQP6 mRNA and protein expression in rats in response to altered acid-base or water balance, Am. J. Physiol. Ren. Physiol. 279 (6) (2000) F1014–F1026.
[71] K. Ishibashi, M. Imai, S. Sasaki, Cellular localization of aquaporin 7 in the rat kidney, Exp. Nephrol. 8 (4–5) (2000) 252–257.
[72] E.N. Atochina-Vasserman, A. Biktasova, E. Abramova, D.S. Cheng, V. V. Polosukhin, et al., Aquaporin 11 insufficiency modulates kidney susceptibility to oxidative stress, Am. J. Physiol. Ren. Physiol. 304 (10) (2013) F1295–F1307.
[73] H. Ren, B. Yang, J.A. Ruiz, O. Efe, T.O. Ilori, J.M. Sands, J.D. Klein, Phosphatase inhibition increases AQP2 accumulation in the rat IMCD apical plasma membrane, Am. J. Physiol. Ren. Physiol. 311 (6) (2016) F1189–F1197.
[74] L. Lei, M. Huang, L. Su, D. Xie, F.A. Mamuya, O. Ham, K. Tsuji, T.G. Păunescu, B. Yang, H.A.J. Lu, Manganese promotes intracellular accumulation of AQP2 via modulating F-actin polymerization and reduces urinary concentration in mice, Am. J. Physiol. Ren. Physiol. 314 (2) (2018) F306–F316.
[75] Y. Matsumura, S. Uchida, T. Rai, S. Sasaki, F. Marumo, Transcriptional regulation of aquaporin-2 water channel gene by cAMP, J. Am. Soc. Nephrol. 8 (6) (1997) 861–867.
[76] H.J. Jung, V. Raghuram, J.W. Lee, M.A. Knepper, Genome-Wide Mapping of DNA Accessibility and Binding Sites for CREB and C/EBPβ in Vasopressin-Sensitive Collecting Duct Cells, J. Am. Soc. Nephrol. 29 (5) (2018) 1490–1500.
[77] M. Ranieri, A. Di Mise, G. Tamma, G. Valenti, Vasopressin-aquaporin-2 pathway: recent advances in understanding water balance disorders, F1000Res. 8 (2019). F1000 Faculty Rev-149.
[78] G. Valenti, G. Tamma, The vasopressin-aquaporin-2 pathway syndromes, Handb. Clin. Neurol. 181 (2021) 249–259.
[79] R. Luo, S. Hu, Q. Liu, M. Han, F. Wang, M. Qiu, S. Li, X. Li, T. Yang, X. Fu, W. Wang, C. Li, Hydrogen sulfide upregulates renal AQP-2 protein expression and promotes urine concentration, FASEB J. 33 (1) (2019) 469–483.
[80] W. Zhao, R. Wang, H2S-induced vasorelaxation and underlying cellular and molecular mechanisms, Am. J. Physiol. Heart Circ. Physiol. 283 (2002) H474–H480.
[81] M. Maruno, H. Kiyosue, S. Tanoue, N. Hongo, S. Matsumoto, H. Mori, et al., Renal arteriovenous shunts: Clinical features, imaging appearance, and transcatheter embolization based on angioarchitecture, Radiographics 36 (2) (2016) 580–595.
[82] K.R. Olson, R.A. Dombkowski, M.J. Russell, M.M. Doellman, S.K. Head, N. L. Whitfield, J.A. Madden, Hydrogen sulfide as an oxygen sensor/transducer in vertebrate hypoxic vasoconstriction and hypoxic vasodilation, J. Exp. Biol. 209 (Pt 20) (2006) 4011–4023.
[83] A.M. Koning, A.R. Frenay, H.G. Leuvenink, H. van Goor, Hydrogen sulfide in renal physiology, disease and transplantation–the smell of renal protection, Nitric Oxide 46 (2015) 37–49.
[84] J. Bełtowski, Hypoxia in the renal medulla: implications for hydrogen sulfide signaling, J. Pharm. Exp. Ther. 334 (2) (2010) 358–363.
[85] K.R. Olson, Hydrogen sulfide as an oxygen sensor, Antioxid. Redox Signal 22 (5) (2015) 377–397.
[86] K.R. Olson, Hydrogen sulfide as an oxygen sensor, Clin. Chem. Lab Med 51 (3) (2013) 623–632.
[87] J. Prieto-Lloret, P.I. Aaronson, Hydrogen Sulfide as an O2 Sensor: A Critical Analysis, Adv. Exp. Med Biol. 967 (2017) 261–276.
[88] H. Teng, B. Wu, K. Zhao, G. Yang, L. Wu, R. Wang, Oxygen-sensitive mitochondrial accumulation of cystathionine β-synthase mediated by Lon protease, Proc. Natl. Acad. Sci. USA 110 (31) (2013) 12679–12684.
[89] K.R. Olson, N.L. Whitfield, Hydrogen sulfide and oxygen sensing in the cardiovascular system, Antioxid. Redox Signal 12 (10) (2010) 1219–1234.
[90] H. Hu, Y. Shi, Q. Chen, W. Yang, H. Zhou, L. Chen, Y. Tang, Y. Zheng, Endogenous hydrogen sulfide is involved in regulation of respiration in medullary slice of neonatal rats, Neuroscience 156 (4) (2008) 1074–1082.
[91] R.A. Dombkowski, M.G. Naylor, E. Shoemaker, M. Smith, E.R. DeLeon, G.F. Stoy, Y. Gao, K.R. Olson, Hydrogen sulfide (H_2S) and hypoxia inhibit salmonid gastrointestinal motility: evidence for H_2S as an oxygen sensor, J. Exp. Biol. 214 (Pt 23) (2011) 4030–4040.
[92] T. Yang, C. Xu, Physiology and Pathophysiology of the Intrarenal Renin-Angiotensin System: An Update, J. Am. Soc. Nephrol. 28 (4) (2017) 1040–1049.
[93] J.H. Fountain, J. Kaur, S.L. Lappin, Physiology, Renin Angiotensin System, StatPearls Publishing,, StatPearls. Treasure Island (FL), 2023.
[94] S.L. Vargas, I. Toma, J.J. Kang, E.J. Meer, J. Peti-Peterdi, Activation of the succinate receptor GPR91 in macula densa cells causes renin release, J. Am. Soc. Nephrol. 20 (5) (2009) 1002–1011.
[95] J. Peti-Peterdi, R.C. Harris, Macula densa sensing and signaling mechanisms of renin release, J. Am. Soc. Nephrol. 21 (7) (2010) 1093–1096.
[96] G. Remuzzi, N. Perico, M. Macia, P. Ruggenenti, The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease, Kidney Int Suppl. 99 (2005) S57–S65.
[97] M.K. Ames, C.E. Atkins, B. Pitt, The renin-angiotensin-aldosterone system and its suppression, J. Vet. Intern Med 33 (2) (2019) 363–382.
[98] J. Peters, K. Münter, M. Bader, E. Hackenthal, J.J. Mullins, D. Ganten, Increased adrenal renin in transgenic hypertensive rats, TGR(mREN2)27, and its regulation by cAMP, angiotensin II, and calcium, J. Clin. Invest 91 (3) (1993) 742–747.
[99] S. Gambaryan, C. Wagner, A. Smolenski, U. Walter, W. Poller, W. Haase, A. Kurtz, S.M. Lohmann, Endogenous or overexpressed cGMP-dependent protein kinases inhibit cAMP-dependent renin release from rat isolated perfused kidney, microdissected glomeruli, and isolated juxtaglomerular cells, Proc. Natl. Acad. Sci. USA 95 (15) (1998) 9003–9008.
[100] U.G. Friis, B.L. Jensen, S. Sethi, D. Andreasen, P.B. Hansen, O. Skott, Control of renin secretion from rat juxtaglomerular cells by cAMP-specific phosphodiesterases, Circ. Res 90 (2002) 996–1003.
[101] U.G. Friis, J. Stubbe, T.R. Uhrenholt, P. Svenningsen, R.M. Nusing, O. Skøtt, B. L. Jensen, Prostaglandin E2 EP2 and EP4 receptor activation mediates cAMP-dependent hyperpolarization and exocytosis of renin in juxtaglomerular cells, Am. J. Physiol. Ren. Physiol. 289 (2005) F989–F997.
[102] M. Lu, Y.H. Liu, H.S. Goh, J.J. Wang, Q.C. Yong, R. Wang, J.S. Bian, Hydrogen sulfide inhibits plasma renin activity, J. Am. Soc. Nephrol. 21 (6) (2010) 993–1002.
[103] M. Lu, Y.H. Liu, C.Y. Ho, C.X. Tiong, J.S. Bian, Hydrogen sulfide regulates cAMP homeostasis and renin degranulation in As4.1 and rat renin-rich kidney cells, Am. J. Physiol. Cell Physiol. 302 (1) (2012) C59–C66.
[104] Y.H. Liu, M. Lu, Z.Z. Xie, F. Hua, L. Xie, J.H. Gao, Y.H. Koh, J.S. Bian, Hydrogen sulfide prevents heart failure development via inhibition of renin release from mast cells in isoproterenol-treated rats, Antioxid. Redox Signal 20 (5) (2014) 759–769.
[105] P. Huang, S. Chen, Y. Wang, J. Liu, Q. Yao, Y. Huang, H. Li, M. Zhu, S. Wang, L. Li, C. Tang, Y. Tao, G. Yang, J. Du, H. Jin, Down-regulated CBS/H2S pathway is involved in high-salt-induced hypertension in Dahl rats, Nitric Oxide 46 (2015) 192–203.
[106] H. Laggner, M. Hermann, H. Esterbauer, M.K. Muellner, M. Exner, B.M. Gmeiner, S. Kapiotis, The novel gaseous vasorelaxant hydrogen sulfide inhibits angiotensin-converting enzyme activity of endothelial cells, J. Hypertens. 25 (10) (2007) 2100–2104.
[107] H. Xue, P. Yuan, J. Ni, C. Li, D. Shao, J. Liu, Y. Shen, Z. Wang, L. Zhou, W. Zhang, Y. Huang, C. Yu, R. Wang, L. Lu, H(2)S inhibits hyperglycemia-induced intrarenal

renin-angiotensin system activation via attenuation of reactive oxygen species generation, PLoS One 8 (9) (2013), e74366.
[108] W. Su, R. Cao, X.Y. Zhang, Y. Guan, Aquaporins in the kidney: physiology and pathophysiology, Am. J. Physiol. Ren. Physiol. 318 (1) (2020) F193–F203. Jan 1.
[109] A. Kharin, E. Klussmann, Many kinases for controlling the water channel aquaporin-2, J. Physiol. (2023), https://doi.org/10.1113/JP284100.
[110] S.Y. Liu, X.C. Duan, S. Jin, X. Teng, L. Xiao, H.M. Xue, Y.M. Wu, Hydrogen Sulfide Improves Myocardial Remodeling via Downregulated Angiotensin II/AT1R Pathway in Renovascular Hypertensive Rats, Am. J. Hypertens. 30 (1) (2017) 67–74.