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Pharmacological Research 161 (2020) 105121

Contents lists available at ScienceDirect

Pharmacological Research

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

H_2S- and NO-releasing gasotransmitter platform: A crosstalk signaling pathway in the treatment of acute kidney injury

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ARTICLE INFO

Keywords:
Acute kidney injury
Hydrogen sulfide
Nitric oxide
Nanomaterials

ABSTRACT

Acute kidney injury (AKI) is a syndrome affecting most patients hospitalized due to kidney disease; it accounts for 15 % of patients hospitalized in intensive care units worldwide. AKI is mainly caused by ischemia and reperfusion (IR) injury, which temporarily obstructs the blood flow, increases inflammation processes and induces oxidative stress. AKI treatments available nowadays present notable disadvantages, mostly for patients with other comorbidities. Thus, it is important to investigate different approaches to help minimizing side effects such as the ones observed in patients subjected to the aforementioned treatments. Therefore, the aim of the current review is to highlight the potential of two endogenous gasotransmitters - hydrogen sulfide (H_2S) and nitric oxide (NO) - and their crosstalk in AKI treatment. Both H_2S and NO are endogenous signalling molecules involved in several physiological and pathophysiological processes, such as the ones taking place in the renal system. Overall, these molecules act by decreasing inflammation, controlling reactive oxygen species (ROS) concentrations, activating/inactivating pro-inflammatory cytokines, as well as promoting vasodilation and decreasing apoptosis, hypertrophy and autophagy. Since these gasotransmitters are found in gaseous state at environmental conditions, they can be directly applied by inhalation, or in combination with H_2S and NO donors, which are compounds capable of releasing these molecules at biological conditions, thus enabling higher stability and slow release of NO and H_2S. Moreover, the combination between these donor compounds and nanomaterials has the potential to enable targeted treatments, reduce side effects and increase the potential of H_2S and NO. Finally, it is essential highlighting challenges to, and perspectives in, pharmacological applications of H_2S and NO to treat AKI, mainly in combination with nanoparticulated delivery platforms.

1. Introduction: pathophysiology of acute renal injury (AKI)

Acute kidney injury (AKI) is defined as a rapid loss of kidney function observed through fast creatinine level increase and urine output decrease, which can last from hours to days [1]. Initially, this syndrome disables electrolyte, acid-base and water balances [2]. Most patients hospitalized with some kidney disease have AKI; these patients account for 10–15 % of all intensive care hospitalizations worldwide [3]. AKI is often silent, since most patients are exposed to other conditions associated with AKI, such as sepsis.

According to the Kidney Disease Improving Global Outcomes (KDIGO), AKI is divided into three main stages associated with stress, damage and dysfunction [4]. At stage 1, creatinine level, an important marker of kidney injury, is ≥ 1.5-fold the baseline or increases to ≥ 0.3 mg/dl within 48 h. At stage 2, creatinine level is ≥ 2-fold the baseline representing damage stage. Finally, at stage 3, creatinine level is ≥ 3-fold the baseline or increases to ≥ 4 mg/dL, or acute dialysis. Urine volume, given as an option to observe the glomerular filtration rate (GFR) and expressed by quantity of urine produced per unit of time (mL/min), can be modulated in all stages, oscillating according to the osmolarity [4].

High incidence and prevalence of advanced AKI stages stood out for over a decade. Advanced and chronic disease stages require dialysis treatment, whereas chronic cases require kidney transplantation [5]. AKI does not present linear progression. AKI stage 1 can lead to chronic kidney disease (CKD) depending on stress severity, whereas CKD can regress the normal stage without going through AKI. It happens when *i)* kidney dysfunctions or damage remain for a long period-of-time without medical diagnosis [6] and *ii)* kidney diseases result from different conditions likely simultaneous to different AKI and CKD stages

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https://doi.org/10.1016/j.phrs.2020.105121
Received 29 June 2020; Received in revised form 29 July 2020; Accepted 31 July 2020
Available online 14 August 2020

[1]. In other words, AKI is not associated with a single disease, but with a set of them, such as sepsis, urinary tract obstruction, inflammation, among others.

Ischemia and reperfusion (IR) injury is the main cause of AKI [7]; it is a temporary blood flow obstruction condition [8]; many IR models have been described in the literature. It is undeniable that IR causes renal tubular injury, as well as increases inflammatory compound and oxidative stress levels, which leads to systemic injury [7]. IR is followed by a re-oxygenation process named reperfusion. Many cascades of deleterious responses (mainly cellular responses) [9], such as oxidative stress and the formation of reactive oxygen species (ROS), take place during reperfusion. These responses are followed by fibrosis and renal remodeling [10].

Renal fibrosis is strongly associated with AKI and CKD. Studies have investigated myofibroblast populations triggering fibrogenic process after the IR. Moreover, these studies associated them with inflammatory processes in the organ [11]. The tight interaction between kidney and heart, called cardiorenal syndrome (CRS), is well-established. Briefly, CRS is described as a spectrum of clinical changes simultaneously involving the heart and kidneys; which leads to a sequence of interdependent events and mechanisms damaging both organs [12–14]. In other words, CRS is a multifactorial, bidirectional and dynamic process.

Several components are released into the systemic circulation during kidney injuries such as AKI; among them, one finds vasopeptides, catecholamines and cytokines, which can induce a series of changes in cardiac tissue and lead to a wide variety of cardiovascular diseases (CVD) [15,16]. Patients with CKD often show increased prevalence of CVDs such as hypertension, peripheral vascular disease and congestive heart failure. In addition, patients with terminal-stage kidney disease present significantly increased cardiovascular morbidity and mortality rates. Although the cellular process and mechanisms involved in AKI have been the subject of considerable interest, they remain poorly understood [17–19].

AKI has many causes; thus, different treatments have been used against it. The most common pharmacological strategies comprise i) Renin-Angiotensin-Aldosterone System (RAAS) blockers and ii) Sympathetic Nervous System (SNS) antagonists, which are capable of improving AKI by enhancing renal hemodynamics and tubule-glomerular feedback, as well as of improving blood pressure levels [20]. In addition to bringing benefits to renal tissue, angiotensin II blockers also avoid heart and inflammatory impairment in unilateral IR model [21]. Antioxidants also play an important role after the IR since they help preventing the deleterious effects of AKI. Lee et al. have described a powerful treatment based on alpha-lipoic acid (ALA), which was capable of eliminating free radicals [22,23]. More recently, another strategy based on the klotho treatment (antioxidant and anti-inflammatory agent) has shown promising results, since its exogenous administration helped preventing AKI [11].

Although important progress has been achieved in studies involving different AKI treatments, few therapies have led to clinical discoveries. Moreover, pharmacological tools have advantages and disadvantages, since patients may have other comorbidities. Thus, it is necessary investigating new approaches to treat AKI with minimum side effects. The aim of this current work is to highlight the recent progress in investigations about the biological effects of two important gasotransmitters - hydrogen sulfide (H_2S) and nitric oxide (NO) – on AKI treatment, as well as their clinical potential to be used in association with nanomaterials.

2. Biological importance of H_2S

H_2S is an endogenous gasotransmitter involved in several physiological and pathophysiological processes taking place in the cardiovascular, neuronal, renal, gastrointestinal and immune systems [24]. Along with NO and carbon monoxide (CO), H_2S is part of a family of endogenous gas mediators; it was the last member identified in this family [25]. Although H_2S has been known as toxic gas for decades, its biochemistry got better understood in recent years. Since H_2S was first described as neuronal modulator in the 1990s [26], there has been intensive research on H_2S biochemistry, which is involved in several biological processes. Under physiological conditions, nitrate and nitrite can be recycled in tissues and blood, leading to NO and several enzymes, such as persulfide dioxygenase, quinone oxireductase, sulfite oxidase and rhodanese, catalyze the oxidation of this gasotransmitter into sulfate and thiosulfate [24, 27–30]. Nowadays, H_2S is acknowledged as an important antioxidant, anti-inflammatory and anti-apoptotic agent [31], although, this molecule has already been shown as a pro-inflammatory agent [32]. NO and H_2S have complex and dichotomy effects in biological system, acting as pro- and anti-inflammatory agents, depending on their concentrations, cell redox state, the disease model evaluated, and the rate of H_2S generated from a donor (thus, H_2S flux is crucial) [32,33]. Generally, at nano to low micromolar concentrations, H_2S acts as anti-oxidant agent, whereas at superior concentrations, opposite effects are observed (pro-inflammatory effects). Indeed, at high concentrations, H_2S donors have been reported to increase the production of inflammatory mediators (IL-1β, IL-6, TNF-α, prostaglandin E2 and NO), while at low concentrations (up to 100 μM), H_2S inhibits their production [33]. For instance, at concentrations between 25–250 μM, H_2S protected human neuroblastoma (SH-SY5Y) cells against peroxynitrite ($ONOO^-$) [34]. In contrast, at higher concentrations (200–500 μM), H_2S caused apoptosis in human aortic smooth muscle cells [35]. Similar to NO, H_2S was first reported to be a pro-inflammatory agent, and during sepsis, patients have been reported to have high levels of H_2S in plasma [33]. At low concentrations, H_2S acts as cytoprotective agent by reducing the expression of pro-inflammatory cytokines, enzymes, and chemokines, and to significantly suppress the activation of nuclear transcription factor-κB (NF- κB). Thus, H_2S has been exploited in the design of effective anti-inflammatory drugs [32]. In this direction, it has been demonstrated that the inhibition of endogenous H_2S production activated inflammatory response and promoted apoptosis in renal IR. In this sense, the effect of H_2S on toll-like receptors-mediated inflammatory pathways in renal IR was evaluated in rats. Toll-like receptors are involved in innate immunity and inflammatory responses. It has been demonstrated that endogenous H_2S has important anti-oxidant effect in rat renal IR by suppressing inflammation and apoptosis by inhibiting the activation of toll-like receptors constitutively expressed in renal tubular epithelial cells [34]. Thus, the majority of recent work have demonstrated H_2S as an anti-inflammatory agent, although further research is still required to better comprehend the two faces of H_2S [36,37]. Particularly, in renal system and under physiological conditions, H_2S regulates the excretory function of the kidney, the release of renin from juxtaglomerular cells, controlling blood pressure. Changes of H_2S concentrations have been associated with important pathological conditions, including IR, diabetic nephropathy, obstructive nephropathy, and hypertensive nephropathy [31].

H_2S is a weak acid that can dissolve in water. Thus, in biological system, the gasotransmitter is dissolved, actuating as solute [31,38]. By considering the pKa value of H_2S under physiological conditions (37 °C, and pH 7.4), H_2S is found as *ca.* 86 % of HS^-, 14 % of H_2S gas and trace of S^{2-} [31,38]. Similar to NO, the lipophilic nature of H_2S allows it to easily diffuse through cell membranes and to act as cell signaling agent [39]. This molecule is significantly synthesized in the kidney, suggesting its importance to the physiological function of this organ [31]. H_2S regulates the excretory activity of the kidneys under normal conditions; it prevents the presence of sodium transporters on tubular cells, as well as the modulation of renin release from juxtaglomerular cells, thus controlling blood pressure. As expected, and similar to NO, pathological renal conditions, such as diabetic nephropathy, renal IR injury, obstructive nephropathy and hypertensive nephropathy, can be associated with changes in H_2S levels [31]. H_2S plays different roles in CKD, whose progression is induced by renal hypoxia; among these

roles, one mainly finds the preservation of medullary oxygenation, prevention of inflammatory response, stabilization of the hypoxia inducible factor and suppression of oxidative stress [40].

Given the important role played by H_2S in biological system, several H_2S donors have been used in biomedical applications to treat different diseases. These donors comprise inorganic sulfide salts such as NaHS (the most used one), nucleoside phosphorothioates, different organic donors, non-steroidal anti-inflammatory drugs, cysteine-derived compounds and even polysulfides deriving from garlic extract [24]. Similar to NO, the use of H_2S-donors/generators has been recently evaluated in the treatment of different diseases such as atherosclerosis, renal and heart failure, pulmonary and arterial hypertension, IR injury, inflammatory conditions, diabetic nephro- and retinopathy, Alzheimer's and Parkinson's disease, sexual dysfunction, among others [24,41]. Interestingly, the anti-inflammatory properties of H_2S donors may be used to mitigate kidney toxicity caused by treatments based on cisplatin, which is an anti-neoplastic drug that causes renal toxicity due to the formation of reactive oxygen species (ROS) [42]. Indeed, H_2S acts by disrupting cisplatin bioconversion into nephrotoxic metabolites due to its anti-inflammatory properties.

In addition to the direct use of H_2S donors to treat these diseases, many drugs can regulate endogenous H_2S levels; these mechanisms have been the object of intensive research. Importantly, recent evidence has suggested crosstalk between NO and H_2S under physiological and pathophysiological conditions [43]. The crosstalk between both gasotransmitters may lead to distinct responses: (i) decrease in the NO and NOS expression and bioavailability, and (ii) NOS functions and NO bioavailability restoration [44–47]. However, it is necessary conducting additional studies to help better understanding this topic, which is further discussed in section 7.

3. Pharmacotherapeutic applications of H_2S donors in AKI

Several studies have investigated the role played by H_2S in AKI. It is well-known that renal cells produce H_2S; however, its production decreases under disease condition [48]. Besides, the role played by H_2S in the cardiovascular system is also object of studies. H_2S is a key player in blood pressure control since it enables vasodilatation and has cardioprotective action [37,49]. Similar to NO, H_2S action as vasodilator depends on its concentration, which can have beneficial and harmful effects on cardiac tissue [24]. The role played by H_2S donors as therapeutic strategy has already been investigated. Studies have suggested the anti-inflammatory and antioxidant activity of H_2S [50]. According to *Kubo et al.*, NaHS (a H_2S donor) is capable of inhibiting endothelial nitric oxide synthase (eNOS) activity and may have systolic effect on blood vessels in the absence of NO [51]. Moreover, changes in H_2S levels have been linked to the development and progression of kidney diseases, from the acute to the chronic stage [41,42,52–55]. In addition, the administration of H_2S donors, in combination with angiotensin, can convert enzyme inhibitors or adrenergic receptor blockers, as well as improve renal function, which turns it into an interesting approach to treat renal fibrosis in CKD [56].

Two strategies can be used to target H_2S in biomedical applications: (i) direct administration of H_2S donors, and (ii) approaches focused on increasing endogenous H_2S production. The aim of this section is to present and discuss the recent progress on the use of H_2S donors against AKI. Strategies focused on increasing endogenous H_2S production have been investigated in several studies [24,31,57]. H_2S donors have been used to treat renal diseases since they help mitigating inflammation, actuate as a ROS scavenger, impair the activation of fibrosis-related cells, decrease cytokine formation, allow vascular remodeling, decrease blood pressure, trigger tubular cell regeneration, as well as decrease apoptosis, hypertrophy and autophagy [58].

Inorganic salt NaHS is the most used H_2S donor. Although important results have been achieved with the use of this donor, NaHS has limitations due to its pharmacokinetic profile and short desirable biological effect [24]. Therefore, the design of long-lasting H_2S donors/generators is an important topic yet under investigation. Several experimental models of renal IR injury have used NaHS as protective agent [24].

Renal IR injury is the major cause of AKI, which is featured by calcium overload, ATP depletion, ROS generation, apoptosis and inflammation [31]. Accordingly, H_2S can mitigate, at least partially, these deleterious effects. Impaired H_2S generation is observed during renal IR injury; thus, the administration of H_2S donors may have positive effects on it [24,31,59]. Indeed, NaHS administration has renal protective effects since it works as anti-apoptotic, anti-inflammatory and antioxidant agent [31]. Likewise, the water-soluble slow-release H_2S donor P-(4-methoxyphenyl)-P-4-morpholinyl-phosphinodithioic acid (GYY4137) can protect tissues from damages by inhibiting the activation of MAPK and NF-κB signaling [60]. Moreover, AP39 (a mitochondria-targeted H_2S donor, namely [10-oxo-10-[4-(3-thioxo-3H-1,2-dithiol-5-yl)phenoxy]decyl]triphenyl-phosphonium) has inhibited ROS formation caused by glucose oxidase and protected kidneys from IR injury in animal models [61].

The impact of H_2S donor AP39 was investigated *in vitro* (kidney epithelial cells of NRK-49 F rats) and *in vivo* (rat model of renal ischemia reperfusion injury) [61]. Cells pre-treated with H_2S donor (30–300 nmol/L) have shown protective effect against glucose oxidase induced by oxidative stress, in a concentration-dependent manner, and mitigated mitochondrial dysfunction. Glucose oxidase has decreased intracellular ATP levels, increased ROS and led to necrosis. These deleterious effects were avoided through cell incubation with AP39. Moreover, rats subjected to renal IR injury have shown high blood creatinine and urea levels, which were seen as damage indicators that have led to increased oxidative stress, enhanced neutrophil infiltration and high plasma IL-12 levels in comparison to the control group. All these pathophysiological changes were mitigated, in a concentration-dependent manner, in rats pre-treated with AP30 (0.1, 0.2 and 0.3 mg/kg); the best results were observed for the highest tested H_2S concentration [61]. AP30 renal protection mechanisms may be associated with its antioxidant effect, which, in its turn, mitigates several feed-forward pathways of oxidative and inflammatory processes.

Besides the renal system, the action of H_2S donors in the cardiovascular system has been investigated. It is worth highlighting the important role played by crosstalk between heart and kidneys in several pathological conditions. Thus, the cardioprotective role played by different H_2S donors (sodium sulfide (Na_2S), thiovaline (TV), GYY4137 and AP39) was investigate in animal models with myocardial failure (ischemia-reperfusion injury) [62]. Interestingly, the authors of the aforementioned study have shown that the beneficial effects of Na_2S were blocked due to nitric oxide synthase (NOS) inhibition, a fact that suggested crosstalk between H_2S and NO. H_2S donors presented different actions in the injury, since they enhanced the phosphorylation of endothelial NOS found in Na_2S treatment, but not under AP39 addition [62]. This result suggests that H_2S donors should be selected for specific applications; however, this issue should be further explored.

H_2S donor has shown beneficial effects on rat model of Crush syndrome, which can lead to AKI [27]. Crush injury was induced through hindlimb compression for 6 h; animals were treated with H_2S donor NaHS (100 mmol/Kg ip). These animals presented reduced kidney injury, as seen in decreased neutrophil gelatinase-associated lipocalin, transforming growth factor-β, tumor necrotizing factor-α and ROS levels, as well as in increased total antioxidant contents in kidneys. Moreover, these animals showed reduced serum urea, creatine kinase and creatinine levels, decreased renal failure and reduced apoptosis upon NaHS treatment in comparison to untreated animals. Thus, NaHS administration helped preventing AKI in animal models with crush injury by reducing oxidative stress, inflammation and apoptosis [27].

The effects of H_2S on contrast-induced AKI were recently evaluated in experiments conducted *in vivo* focused on investigating endogenous H_2S up-regulation [63]. Experiments *in vitro* were also performed; NRK-52E rat kidney epithelial-like cells were treated with iopromide (to create contrast-induced AKI), which was followed by NaHS

administration. Significant improvement in renal dysfunction and morphological changes were observed in animals treated with atorvastatin in comparison to the control group; it also reduced ROS formation, inflammation and apoptosis. Furthermore, increased serum H_2S levels and renal expression of cystathionine γ-lyase and cystathionine-β synthase (two H_2S synthetases) were reported. Results *in vitro* have shown that cells incubated with NaHS presented considerably reduced inflammation and cell death levels in comparison to the control group. Thus, the renal protection effects of atorvastatin derive from the H_2S pathway [63]. Further studies are required to help better understanding this mechanism.

H_2S can have anti- or pro-inflammatory effects, depending on its flow (concentration and action time) and on the redox state of the biological site. For instance, rats were treated with NaHS (2 mg/kg) in a study conducted with animal models presenting endotoxemia. Short course infusion of H_2S donor was capable of reducing kidney and lung injury, whereas the opposite effect was observed for systemic NaHS infusion; this case showed increased pro-inflammatory response - elevated TNF-α and IL-10 levels were observed during endotoxemia [64]. Therefore, caution must be taken with H_2S doses in biomedical applications.

4. Biological importance of NO in AKI

AKI and CVD share common pathological pathways and factors such as oxidative stress. In mechanistic terms, oxidative stress and NOS system lead to endothelial dysfunction and reduced NO bioavailability, as observed during CRS [65]. NO is produced in the body through the action of three NOS isoforms that are divided into two groups, namely: constitutive (neural- nNOS and endothelial-eNOS) and inducible (iNOS) [66]. NOS produces NO through oxidation of *L*-arginine to *L*-citrulline. NO and its oxidized products (NOx) are capable of changing different macromolecules such as proteins, lipids and nucleic acids in order to produce both physiological and pathophysiological effects [67]. Healthy renal function depends on the balance ROS and NO metabolism [68].

Similar to H_2S, NO plays an important role in kidney function, since this free radical is involved in processes such as the regulation of renal hemodynamics, modulation of medullary blood flow, mediation of pressure-natriuresis, blunting of tubuloglomerular feedback, modulation of renal sympathetic neural activity and inhibition of tubular sodium reabsorption [69]. Human body must function at normal NO level, based on each tissue type. High NO levels (in the micro-milli molar range) can inhibit mitochondrial respiration due to competition for mitochondrial cytochrome oxidase oxygen [68]; in addition, it is associated with endothelial function progression in hypertensive patients [70]. On the other hand, NO deficiency has already been associated with AKI progression to CKD and with hypertension. Reduced plasma NO concentrations have been observed in hypertensive patients [71], whereas transgenic (TG) mice knocked out by eNOS have spontaneously developed hypertension [72]. It becomes evident that interventions in redox imbalance and NO bioactivity can lead to promising therapeutic strategies [65,73]. Thus, recent progress in NO donor administration to treat AKI will be presented in the next section.

5. NO-based pharmacotherapy applications in AKI

This section highlights publications selected based on the recent progress in NO/NO donor application in individuals with acute renal failure. Direct NO gas administration can be used in clinical settings, since it can enhance arterial oxygenation in patients with acute respiratory distress syndrome [74]. NO gas administration in newborns treated for pulmonary hypertension is approved by the US Food and Drug Administration (FDA), and it can be used as recue treatment in patients with hypoxic COVID-19 symptoms [75]. Accordingly, Gozdzik et al. observed the beneficial effects of inhaled NO (initial 80 ppm dose followed by 30 ppm) used in association with intravenous steroid administration (corticosteroids, 25 mg x 3) in IR injury models with aortic clamping. The authors observed that hydrocortisone and inhaled NO administration decreased kidney messenger RNA toll-like receptor 4 expression to pre-ischemic conditions; in addition, it significantly improved systemic hemodynamics and tissue oxygenation, as well as decreased the systemic inflammatory response [75].

An observational study was conducted to investigate the association between inhaled NO therapy and the incidence of AKI in patients subjected to lung transplantation. It was done by taking into consideration that NO gas-based therapy is often applied to lung transplantation recipients in clinical settings and that AKI plays a critical role in the prognosis of lung transplantation recipients [75]. The authors did not find correlation between inhaled NO therapy and incidence of poslung transplantation AKI. Inhaled NO plays an important role in lung transplantation cases since it significantly enhances lung oxygenation, reduces pulmonary vascular resistance, prevents reperfusion injury and does not have side effects on kidneys. On the contrary, inhaled NO has positive effects on renal, hepatic and splanchnic perfusion [75].

Besides the direct gaseous NO administration, NO donors/generators have been used in several biomedical applications such as AKI treatment. Thus, nitrate or nitrite intake can increase the NO levels and have cardiorenal-protective effects on animal models with cardiorenal diseases such as IR injury [65,76]. Under physiological conditions, nitrate and nitrite can be recycled in tissues and blood, leading to NO and other nitrogenated species with bioactivity [77,78]. This pathway might lead to the formation of nitrogen dioxide (NO_2), which can dimerize forming dinitrogen tetroxide (N_2O_4) that is hydrolyzed producing equimolar amounts of nitrate and nitrite. Moreover, NO_2 can react with NO leading to the formation of dinitrogen trioxide (N_2O_3), a nitrosating agent, which can be hydrolyzed to nitrite, thus reactive intermediates can also be formed [80]. Nitrite has shown beneficial effects on renal IR injury in mice, whose vasodilation has significantly enhanced during hypoxia at low pH [79]. Interestingly, the acidic environment found in hypoxic tissues enabled nitrite reduction to NO since nitrite protonation produces nitrous acid, which forms N_2O_3 that undergoes disproportionation, leading to the formation of NO and NO_2 [17]. In general, as these mechanisms are enhanced during hypoxia and acidosis, they represent an important pathway, as NOS activity may be compromised in such conditions [80]. In these specific conditions, the nitrite reduction to NO has shown positive effects, such as cellular response to ischemic stress, hypoxic signaling, and vasodilation [81,82]. Based on similar approach applied to experimental rat models with crush syndrome, sodium nitrite (200 mmol/Kg) administration prevented damages associated with IR injury by decreasing systemic inflammation [83].

Red beets and leafy greens are rich in nitrate, which can be reduced to nitrite and NO in the human body due to the action of enzymes such as xanthine oxidoreductase [76,84]. Nitrate-nitrite-NO pathway has important antioxidant and anti-inflammatory effects. Thus, chronic supplementation with inorganic nitrate/nitrate is indicated for several renal and cardiovascular conditions [65]. Indeed, nitrate-rich beetroot intake helped lowering the renal resistive index and blood pressure in patients with kidney disease [85]. Ingested nitrate is concentrated and secreted into the oral cavity by salivary glands, and reduced to nitrite by oral bacteria, followed by its absorption by the upper intestine [86]. Saliva containing nitrite is absorbed in the stomach and enters the blood stream, where it is reduced to NO by different NO reductase pathways [67]. However, caution must be taken with nitrate-based supplementation since certain concentrations of it may lead to increased oxidative stress and endothelial dysfunction, as well as impair kidney function [87].

To overcome this issue, in a different approach, the NO donor (5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one, EDV), characterized by a furoxan moiety of edaravone, was evaluated in renal IR injury [88]. EDV is a free-radical scavenger known to mitigate organ ischemic

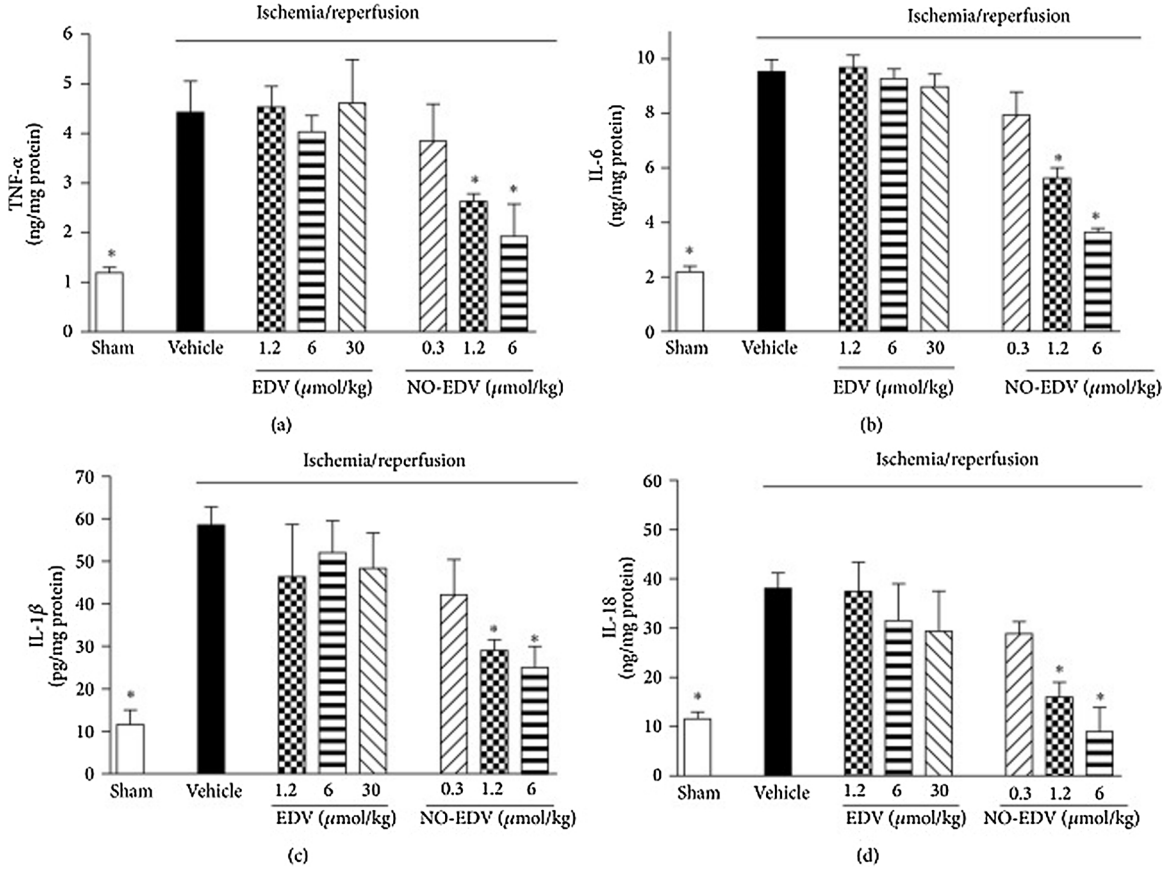

Fig. 1. Effects of EDV and NO-EDV on cytokine production in kidney samples. TNF-α (a), IL-6 (b), IL-1β (c), and IL-18 (d) levels were measured in the kidney of sham-operated rats (sham) and rats that underwent 45 min ischemia and 6 h reperfusion in the absence (vehicle) or presence of EDV (1.2–30 μmol/kg, i.v.) or NO-EDV (0.3–6 μmol/kg, i.v.). Data are mean S.E.M. $^{*}P < 0.05$ *versus* vehicle. Reproduced from Chiazza et al. 2015 under the Creative Commons Attribution License of open access article [88].

injury. NO was coupled to EDV yielding NO-EDV. Wistar rats were subjected to renal IR, and treated with EDV (1.2–6–30 μmol/kg, *i.v.)* or NO-EDV (0.3–1.2–6 μmol/kg, *i.v.*). Both treatments were capable of mitigating renal dysfunction, in a concentration-dependent manner, as seen in serum creatinine and urea, urine flow, creatinine clearance, neutrophil gelatinase-associated lipocalin/lipocalin-2 and urinary *N*-acetyl-β-D-glucosaminidase levels. However, NO-EDV was more effective as protective agent than EDV, since NO-EDV presented renal protection effects at dose-range 1.2–6.0 μmol/kg, whereas higher EDV dose (30 μmol/kg) was necessary to obtain the same protection effect. Moreover, NO-EDV and EDV have modulated oxidative stress and lipid peroxidation in renal tissue. Only NO-EDV has enabled blunted IR up-regulation of inducible NOS, activated endothelial NOS, and inhibited the overproduction of proinflammatory cytokines such as IL-1β, IL-18, IL-6, and TNF-α (Fig. 1) [88]. Together, these results have suggested that NO-donor EDV codrugs can be used as pharmacological approach to treat AKI.

Organic mononitrites of 1,2-propanediol (PDNO), which are capable of generating NO in the blood stream, were synthesized and used to treat AKI in sheep with renal IR injury [89]. Intravenous PDNO infusion has significantly increased creatinine clearance and diuresis in kidneys (Fig. 2), as well as enhanced renal oxygen and decreased mean arterial blood pressure, in comparison to the control group. Overall, PDNO was capable of enhancing renal function after ischemia [89].

S-nitrosothiols (RSNOs), such as S-nitrosoglutathione (GSNO), act as spontaneous NO donors due to homolytic S—N cleavage with free NO release [90]. In biological medium, RSNOs can be decomposed by different mechanisms, such as: heat, ultraviolet light, nucleophiles, metal ions, and other agents that may lead either to homolytic or to heterolytic cleavages [91]. Despite being able to release NO in biological medium, S-nitrosothiols stand out due to the transnitrosylation reactions rather than the S—N cleavage for NO release [92]. Proteins nearby RSNOs or even NO generated from NOS, may interact with RSNOs leading to protein-SNOs [93]. Thus, small RSNOs such as GSNO may transfer the NO group from one thiol to another (S—NO → protein thiols), leading to S-nitrosated proteins, which is a mechanism dependent on the cell's surrounding chemical environment [93]. GSNO is an endogenous molecule that increases NO bioavailability and has NO-like activity, such as vasodilation [94], anti-oxidant effects [95], tissue repair [96,97], anti-microbial activity [98,99], among others. GSNO (50 μg/kg body weight) has shown renoprotective effects on the treatment of sepsis-induced AKI applied to rat models with lipopolysaccharide-induced sepsis [100]. GSNO-treatment applied to LPS-challenged animals has significantly increased IL-10, PPAR-γ and GSH levels, as well as reduced caspase-3, iNOS, TNF-α,T lymphocyte infiltration, in comparison to the untreated animals [100]. Similarly, S-nitrosated human serum albumin (50 μM) has shown protective effects in animal models with kidney disease by inhibiting fibrosis factors such as IL-6 and TGF-β, decreasing oxidative stress and increasing erythropoietin (anti-fibrosis factor) and VEGF expression [101].

Sodium nitroprusside (SNP) is a well-know NO donor [90]. Renal protective effects of SNP, losartan (angiotensin II type 1 receptor antagonist), captopril, and BQ-123 (endothelin type A receptor antagonist) in rat models with renal IR injury were evaluated [102]. SNP and losartan have shown the highest therapeutic potential to mitigate the deleterious effects of acute renal damage and renal function impairment. Moreover, rats treated with NG-nitro-*L*-arginine-methyl ester (*L*-NAME), which is a NOS inhibitor, developed prominent lesions in the

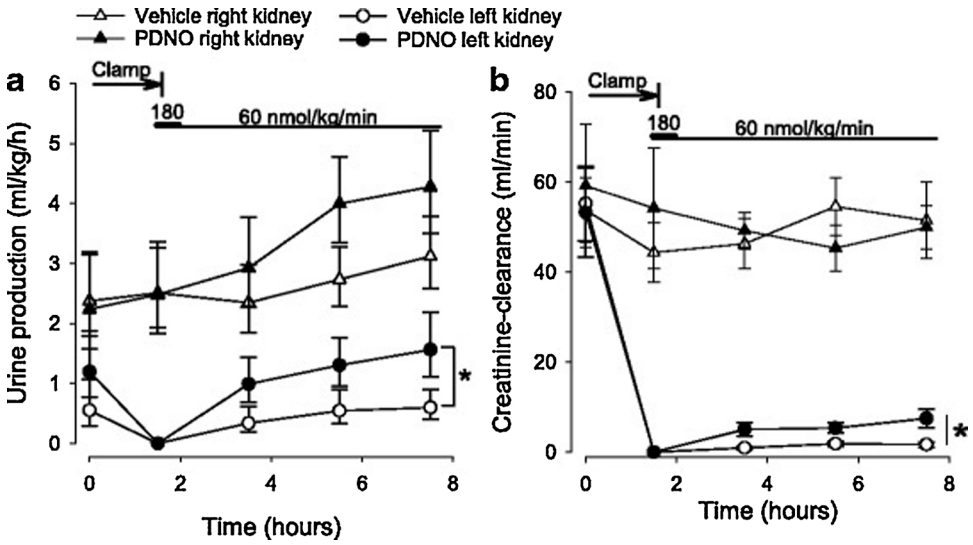

Fig. 2. Urine output (a) and creatinine clearance (b) in 16 anesthetized sheep subjected to left renal ischemia and reperfusion. Renal ischemia was caused by clamping of the renal artery for 90 min. Fifteen minutes prior to the release of the clamp, intravenous infusions with either the organic mononitrites of 1,2-propanediol (PDNO, n = 8) or vehicle (1,2-propanediol + inorganic nitrite, n = 8) were commenced. The infusions continued for 6 h. Data are expressed as mean and SEM. Significant ($p < 0.05$) differences in response to PDNO compared to vehicle is indicated by an asterisk. Reproduced from Nilsson et al. 2017 under the Creative Commons Attribution 4.0 License of open access article [89].

kidney tissue, along with significantly reduced Na-K ATPase activity [102].

Glutamyl-protected *N*-hydroxyguanidine NO donor drugs were prepared and used in individuals with acute renal failure [103]. Synthesized *N*-hydroxyguanidine NO donor drugs were effective against spontaneous NO release due to linkage to glutamyl adducts that can be cleaved by γ-glutamyl transpeptidase (γ-GT), which, in its turn, is mainly found in renal tissue. This prodrug acted as an important vasodilator in isolated perfused rat kidneys (EC50 ~ 50 μM), since it prevented the damaging effects of vasoconstriction on individuals with acute renal failure [103].

Important progress has been achieved due to NO/NO donor administration in several AKI models *in vitro* and *in vivo*. Table 1 summarizes the main results referring to H_2S and NO use in AKI.

6. Challenges and potential uses of H_2S/NO-releasing nanomaterials in AKI

The spatiotemporal controlled generation of gasotransmitters such as H_2S and/or NO is highly desirable to avoid side effects such as systemic blood pressure decrease, and to enhance the therapeutic effects of H_2S or NO on target organs such as kidneys. The development of different classes of H_2S and NO donors represented an important pharmacological progress that has enabled the broad use of these gasotransmitters, in comparison to the direct applications in their gas form, which presents clinical limitations. In addition, there are different classes of H_2S and NO donors that have short and long-lasting half-life [90,104]. An overview of potential applications of both gasotransmitters (H_2S and NO) is schematically represented in Fig. 3.

Although important progress has been achieved in H_2S or NO administration in a wide range of diseases such as kidney injury, H_2S- or NO-based therapies still face limitations in clinical settings due to lack of effective approaches capable of properly delivering these gasotransmitters to a specific organ, such as kidneys. The major issues associated with H_2S and NO administration in medical applications can be summarized as: (i) uncontrolled gasotransmitter release, either too fast or too slow, mainly in the case of H_2S donors; H_2S release mechanism remains poorly known, and (ii) in the case of H_2S, some donors (such as thioisocyanates, thioamides, dithioperoxyanhydrides) can deplete biological thiols generating H_2S. Low and controlled H_2S donor concentrations should be used (nano- low micro molar) due to the biological concentrations of endogenous thiols, such as glutathione at milimolar levels. Caution must be taken in the use of H_2S donors in order to avoid excessive consumption of endogenous free thiols and, consequently, significant changes in the thiol redox balance [105]. The combination between H_2S/NO donors and nanomaterials is a promising approach that has been subjected to intensive investigation focused on helping to overcome these issues.

Overall, advantages of combining H_2S/NO with nanomaterials lie on the likelihood to: (i) promote the sustained release/generation of therapeutic amounts of these gasotransmitters; (ii) target the nanomaterial towards the desired organ, depending on the chemical nature of the nanomaterial; (iii) adapt H_2S or NO concentrations to the amounts necessary to enable successful therapy; (iv) co-administrate H_2S or NO with other pharmacological agents in a given nanomaterial in order to achieve synergist effect; and (v) conjugate H_2S or NO to nanoparticles that intrinsically have therapeutic effects. These progresses may enhance the effectiveness of H_2S or NO, with minimum side effects. There has been intensive research focused on designing smart nanovehicles capable of releasing active agents upon external stimuli such as pH, presence of some enzymes, light, oxygen tension, redox state of the environment, temperature, among others, in recent years [106]. It has already been reported that NO donors encapsulated in polymeric and metallic nanoparticles present slow and sustained release. Alginate nanoparticles containing S-nitroso-mercaptosuccinic acid promoted sustained NO release for 12 h, which improved antibacterial applications [107]. Similarly, GSNO encapsulated in chitosan nanoparticles also evidenced sustained release through Fickian-diffusion and reached a *plateau* after 4 monitoring hours [108]. Moreover, the encapsulation of tert-dodecane S-nitrosothiol donor in co-polymer nanoparticles did not change the NO release profile; it actually enabled photoactivated NO release, which promoted vascular hyperpermeability [109].

Although this topic is poorly explored, few publications have indicated promising nanoparticle applications to enable controlled H_2S release. Another interesting approach lies on the use of H_2S donors-containing mesoporous silica nanoparticles [110,111]. The incorporation of H_2S donors in mesoporous silica nanoparticles enabled a sustained H_2S release in cell culture medium and in rat plasma for 24 and 72 h, respectively. The incorporation of H_2S donor into the nanomaterial was considered as a superior effective strategy in comparison to the free GYY4137 H_2S donor (non-encapsulated), enabling a controlled and slow H_2S generation from the nanomaterial [110,111]. Besides, near infrared-controlled H_2S release by using upconversion nanoparticles based on $LiYF_4$:Yb/Tm and carried with propane-2,2-diylbis ((1-(4,5-dimethoxy-2-nitrophenyl)ethyl)sulfane) as innovative H_2S donor was also suggested [112]. Results have evidenced that nanoparticle irradiation with 980-nm laser enabled H_2S release in a spatially- and temporally controlled manner, as well as opened room for several biomedical applications such as AKI.

Although several important publications have described the

Table 1
Summary of recent progress of using H_2S- and NO-based treatment to AKI.

Specie	Donor molecule	Concentration	Model	Main biological effects	Ref
H_2S	AP39	30 – 300 nM, 0.1 – 0.3 mg/kg	*In vitro* kidney epithelial cell (NRK-F), *in vivo* rat reperfusion model	Inhibition of ROS caused by glucose oxidation and protection from ischemia	[46]
	GYY4137	12.5–50 mg/(kg · day)	*In vivo* male Sprague-Dawley rats reperfusion model	Protective effects against reperfusion injury through attenuation of oxidative stress and apoptosis	[45]
	Na_2S, TV, GYY4137, AP39	1 μmol/L, 4 μmol/L, 26 μmol/L, and 250 nmol/L, respectively	Ischemia-reperfusion injury animal model	Important results were observed regarding NOS inhibition and phosphorylation	[47]
	NaHS	400 – 800 μmol/L	*In vitro* and *in vivo* contrast-induced acute kidney injury models	Considerable reduction in levels of inflammation and cell death	[48]
	NaHS	100 μmol/kg	Acute kidney injury animal model	Decrease of neutrophil gelatinase-associated lipocalin, tumor necrotizing factor-α, ROS and increase of antioxidative levels	[27]
	NaHS	2 mg/kg	Animal model of endotoxemia	pro-inflammatory was observed by higher levels of TNF-α and IL-10	[49]
NO	Inhaled NO	During surgery	Patients with acute lung injuries undergoing lung transplantation	Inhaled NO demonstrated positive effects on renal, hepatic and splanchnic perfusion	[80]
	Nitrite	10^{-9}-10^{-4} mol/L	Mice model of ischemia-reperfusion injury	Vasodilation effects due to nitrite was significantly enhanced during hypoxia with low pH	[81]
	Nitrite	200 mmol/kg	Rat experimental model of crush syndrome	Inflammation decrease and prevention of damages associated with ischemic injury	[63]
	Beetroot juice	300 mg	Patients with kidney disease	Treatment led to lower renal resistive index and blood pressure	[65]
	NO-EDV	1.2; 6 and 30 μmol/kg	Rat model of renal ischemia and reperfusion	Mitigation of renal dysfunction, in a concentration dependent manner. Protective effect in higher concentration.	[68]
	PDNO	60 – 180 nmol/(kg ˙min)	Sheep mode of kidney ischemia and reperfusion	Increased creatinine clearance, diuresis, renal oxygen and decreased mean arterial blood pressured	[69]
	GSNO	50 μg/kg	Rat mode of lipopolysaccharide-induced sepsis	Renoprotective effects by inhibiting fibrosis factors	[77]
	S-nitrosated HSA	50 μmol/L	Kidney disease rat model	Protective effect through the inhibition of IL-6 and TGF-β, decreasing oxidative stress	[78]
	SNP	Pre-treatment (5 mg/kg), post-treatment (10 μg/kg ˙min)	Pat model of renal ischemia-reperfusion	Alleviation of deleterious effects, NOS inhibition and reduction in the Na-K ATPase activity	[79]
	Glutamyl-protected N-hydroxyguanidin	50 μmol/L	Rat isolated perfused kidneys	Prevention of the damaging effects of vasoconstriction in acute renal failure	[82]

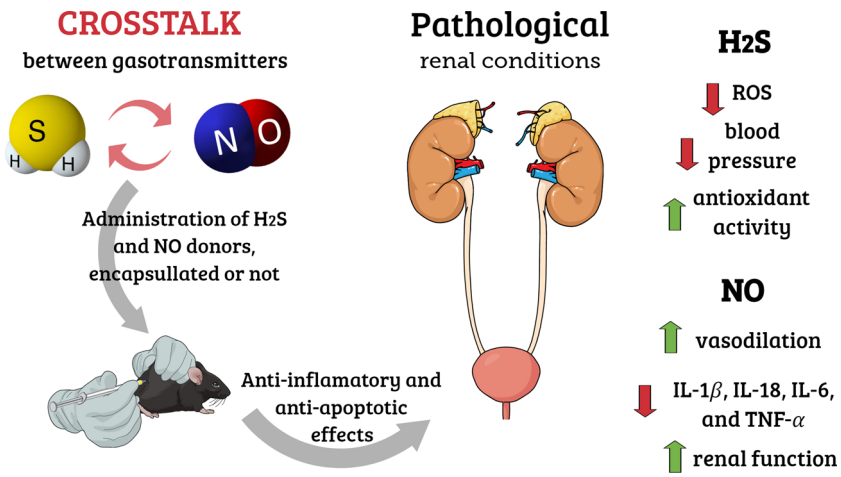

Fig. 3. Schematic representation of potential benefits of exogenous administration of H_2S and NO, and their beneficial effects in kidney.

preparation and uses of H_2S and NO-releasing nanomaterials in different biomedical applications [113,114], their use in AKI remain poorly explored. Moreover, nanoparticles comprising both H_2S and NO donors may have beneficial effects on different pathologies and should be further explored. The crosstalk between H_2S and NO appears to have key regulatory effects on some pathophysiological conditions. Both H_2S and NO donors can mitigate the deleterious effects of AKI. Several important studies have suggested the likely interaction between these two gases to control important biological processes. Interestingly, H_2S pathway appears to be significantly relevant when NO bioactivity is impaired [25]. It is necessary conducting further studies to help better understanding the association between H_2S and NO under normal and pathological conditions. We hope the present review opens new room for the progress of smart and versatile nanomaterials capable of generating H_2S and/or NO in AKI treatment.

7. Crosstalk between gasotransmitters: possible mechanisms of interaction between H_2S and NO and the biological consequences

There are three different gasotransmitters in biological system, namely: CO, NO and H_2S; they can interact with each other, affecting their availability and reactivity [115]. Although their interaction mechanism is not fully understood, most studies overall focus on investigating the crosstalk between NO and H_2S in cardiovascular system [116–118]. It is well-known that NO and H_2S present comparable biological profiles, enable cell protection and act in signaling pathways [44]. The first study about this intercommunication was published in 2006; the authors have shown that H_2S was capable of inhibiting the sodium nitroprusside (SNP) mechanism in aorta relaxation [119]. More recently, a study has evidenced that H_2S interacts with NO and forms small S-nitrosothiol compounds such as thionitrous acid (HSNO), besides nitroxyl (HNO) and other unknown compounds [116], as shown in Fig. 4. However, further studies on this topic are necessary.

NO has shown pro- and anti-inflammatory properties intrinsically associated with its concentration and application site [116]. With respect to H_2S, it was firstly hypothesized that this gasotransmitter plays pro-inflammatory role; although it is well-known that in order to have functions similar to those of NO, it also acts as anti-inflammatory agent [32]. Two different articles have shown that the administration of the H_2S donor inhibits NO overproduction and, simultaneously, enables the inhibition of pro-inflammatory mediators such as IL-1β, IL-6, TNF-α. This outcome indicates the possible positive effect on inflammation resulting from the crosstalk between H_2S and NO [117,118]. Interestingly, opposite effects were also observed in different models. Investigations conducted with endothelial cells have evidenced that the exogenous administration of the H_2S donor (NaHS) has directly

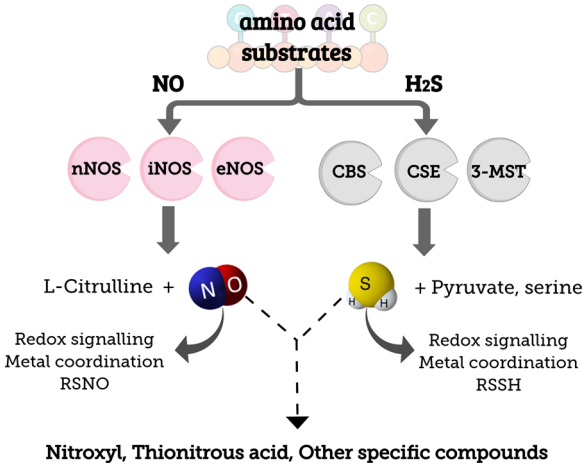

Fig. 4. Schematic representation of the biosynthesis of NO, mediated by nitric oxide synthase isoforms: neuronal, inducible and endothelial (nNOS, iNOS, eNOS, respectively) and the biosynthesis of H_2S, mediated by cystathionine β-synthase, cystathionine γ-lyase and 3-mercaptopyruvate sulfotransferase (CBS, CSE, 3-MST, respectively). Further, the products resultant from the interaction between the two signaling molecules are shown.

increased NO levels due to eNOS stimulation; this process has potentiated proliferative effects on endothelial cells [120]. Still, acute H_2S therapy has successfully restored NO concentration and eNOS functions in individuals with IR injury, which suggested cytoprotective signaling-dependent pathway in NO production stimulation [44].

Data about the interaction between gasotransmitters in renal injuries remain scarce in the literature. A decade ago, two different research groups have evidenced that the crosstalk between NO and H_2S had the potential to mitigate renal damages induced by IR, mostly through iNOS activation by exogenous H_2S administration [121,122]. These results have been supported by recent studies about exogenous H_2S administration, whose promising effects on chronic kidney injury in animal models were evaluated, by taking into consideration the presence and absence of NOS inhibitor [123]. Overall, this treatment protected the animal models from kidney injuries, mostly due to improved antioxidant/oxidant balance, reduced apoptosis and autophagy and decreased number of genes associated with inflammation. Moreover, the authors of the aforementioned study suggested that NO plays an intrinsic role in H_2S-induced renoprotection *via* the previously described patterns; they concluded that NOS isoforms can reduce kidney damage [123]. Although this pathway is not fully understood, these authors have also suggested that NOS isoforms can accelerate chronic

kidney damage depending on their concentration and site; however, further studies should be conducted to help better understanding this mechanism. Similar pattern was also observed for renal injury model induced by gentamicin and treated with exogenous H_2S donor, in the presence and absence of CO synthesis inhibitor [124]. The treatment was capable of reducing renal NO levels and iNOS isoform over-expression, as well as of preventing eNOS degradation and inducing its phosphorylation. Interestingly, this crosstalk was capable of minimizing toxic peroxynitrite formation and, at the same time, it promoted ideal NO release enough to enable blood vessel dilation [124]. Moreover, the authors have shown that effects of H_2S were minimized in the presence of CO inhibitor, suggesting that all three gasotransmitters presented important and linked pathways in the biological system [124].

Little is known about the interaction mechanism among H_2S, NO and CO in biological systems, under different conditions, sites and concentrations. H_2S acts as reducing and nucleophilic agent under physiological conditions, which might react with several NO-derived species [122]. H_2S can lead to chemical complexes with S-nitrosothiols, nitrite, nitrate and peroxinitrates [122]. In fact, some studies have proposed a chemical interaction between NO and H_2S in biological system [125–127]. The interaction between H_2S and nitrogenated species produces two different intermediates: thionitrous acid (HSNO) and nitroxyl (HNO), as demonstrated in Fig. 5 [125]. HNO is known to induces vasodilation, *via* multiple mechanisms, including *via* activation of cyclic guanilyl monophosphate (cGMP)-dependent pathway [35]. Moreover, HNO intermediate generated is responsible for modifying the functions of proteins, mostly by two different routes: (i) by forming disulfide bonds between thiol groups, or (ii) converting thiolated groups (RSH) in cysteine residues into N-hydroxysulfenamide (RSNHOH) [127–129]. This pathway has been mostly studied due to the interesting mechanisms regarding the intermediates HSNO and HNO in the cardiovascular system [127]. HNO is very reactive with thiol-containing biomolecules, forming sulfinamides or disulfides [126].

Considering the interaction previously described in Fig. 4, the crosstalk between *L*-arginine/NO and *L*-cysteine/H_2S was overviewed in a schematic representation (Fig. 6). Through different possible mechanisms, such as H_2S binding to Zn-containing enzymes and/or S-sulfhydration reactions, the phosphodiesterase (PDE) activity is

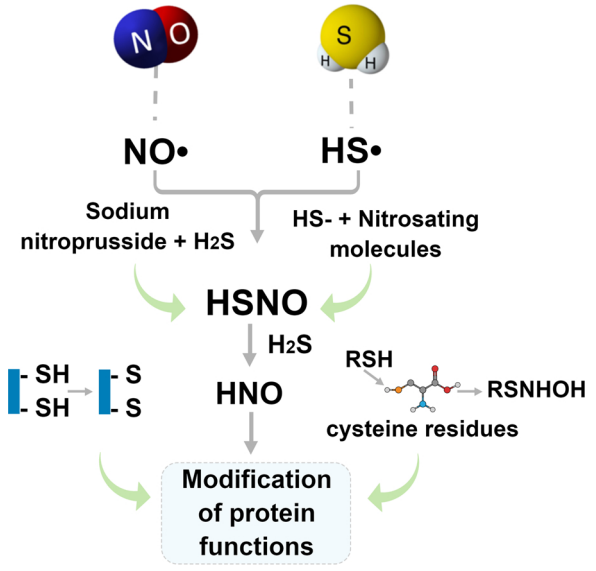

Fig. 5. Schematic representation of the chemical crosstalk between NO and H_2S. From the NO˙ and HS˙ the intermediates HSNO and HNO (nitroxyl) are formed, directly influencing in the protein functions by two distinct pathways: (i) induction of disulfide bonds and (ii) conversion of thiolated groups in cysteine residues to *N*-hydroxysulfenamide (RSNHOH).

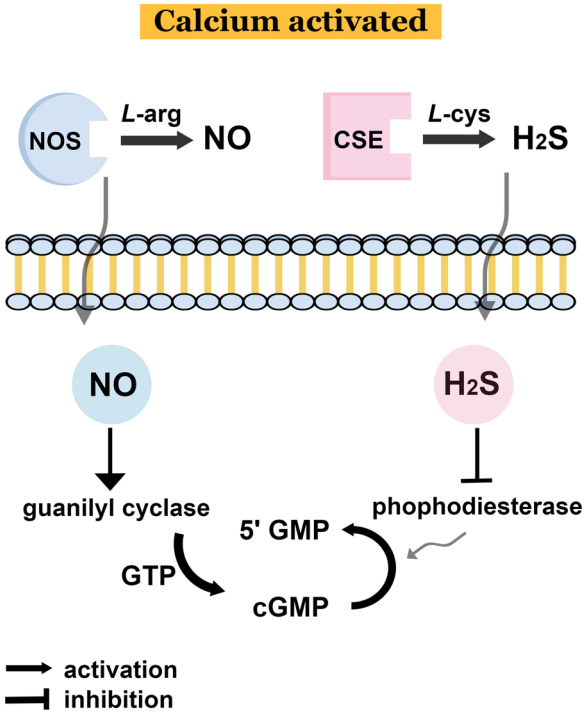

Fig. 6. Schematic representation of the endogenous crosstalk between *L*-arginine/NO and **L**-cysteine/H_2S leading to an increased expression of cGMP and 5′GMP, with direct consequence in hyperpolarization and relaxation. 5′GMP: (5′ guanilyl monophosphate); cGMP: (cyclic guanilyl monophosphate); GTP: guanilyl triphosphate; NOS: nitric oxide synthase; CSE: cystathionine gamma lyase.

inhibited by H_2S [34]. This inhibition directly enhances the expression of cGMP and 5′GMP (5′ guanilyl monophosphate) [34]. Thus, H_2S can modify some cysteine residues impairing PDE activity and enhancing cGMP/protein kinase G signaling [123]. Regarding NO, the activation of guanilyl cyclase increases the guanilyl triphosphate increasing the expression of cGMP and 5′GMP, evidencing the crosstalk between both species with direct consequences in hyperpolarization and relaxation [126]. Administration of exogenous H_2S increased cGMP levels in time/concentration dependent manner. In the endothelium, H_2S inhibits PDE enhancing cGMP accumulation [123]. Indeed, NO and H_2S are both necessary to elicit vasodilation and angiogenesis by converging at cGMP. Increase in intracellular levels of cGMP, in a NO-dependent manner, was observed upon exposure endothelial cells to H_2S, in addition to the activation of protein kinase G (PKG). In other words, both H_2S and NO mutually control vascular function by enhancing intracellular levels of cGMP, which is essential for PKG, angiogenesis and dilation of blood vessels. Moreover, *in vivo* studies confirmed that NO- and H_2S-induced vasorelaxation is cooperative on the cGMP pathway, and both gasotransmitters are required for angiogenesis [130].

In a further study, rabbits subjected to IR and treated with NaHS presented increased levels of cardiac cGMP and reduction of infarct size [131]. These results reinforced that H_2S donors have cardioprotective effects *via* cGMP/PKG pathway by activating NOS, which in turn generates NO. In fact, H_2S facilitates NO-mediated cellular signaling events [132,133]. It is assumed that H_2S stabilizes soluble guanylate cyclase (sGC) in its NO-responsive form. By inhibiting vascular cGMP phosphodiesterase, H_2S can prolong the bioavailability of cGMP. Moreover, polysulfides (derived from H_2S) active cGMP-dependent PKG [133]. Finally, NO and H_2S interaction might also affect each other synthesizing enzymes affecting their generation [134]. For more detailed discussion and mechanisms regarding the convergence of NO and H_2S in biological system, we recommend important review articles in this topic [25,95,133,134].

Although several progresses have been achieved pointing the crosstalk between H_2S and NO, much work still need to be done.

Overall, the reports selected for the current review highlight the potential of these gasotransmitters and the importance of better understanding the roles played by them under different physiological and pathological conditions. It is clear that treatments based on the use of exogenous H_2S or NO donors can have beneficial effects on individuals with renal injury; however, it is necessary conducting further studies to help better understanding this mechanism and enabling advances in this field. It should be noted that as several important works have demonstrated the convergence of the NO and H_2S signaling pathways in cardio/renal diseases, administration of either NO or H_2S donors, individually, might not be sufficient to restore vascular homeostasis. In this sense, the supplementation of both gasotransmitters might have a superior therapeutic effect in the treatment of several vascular dysfunctions. Moreover, the articles analyzed in this review did not evaluate the likelihood of a controlled and targeted release promoted by the association of H_2S and NO with nanoparticles. Since this mechanism depends on the concentration of each gasotransmitter, it is expected that different release approaches can lead to different roles of the gasotransmitters, which may help improving their applications in renal injuries and other pathologies.

8. Conclusion and perspectives

Either H_2S or NO plays a key role in AKI. Although relevant progress has been achieved in understanding the role played by H_2S/NO in pathological conditions, as the ones presented in the current study, it is necessary conducting further investigations to help better understand their action mechanisms, as well as to clarify the association between these gasotransmitters under physiological and pathological conditions. The combination of H_2S- and/or NO- donors with nanomaterials may enable designing new and versatile materials that can be translated into therapeutically useful approaches to treat several diseases such as renal failure. Finally, both H_2S and NO can have positive effects on AKI, although further studies focused on underlying the molecular interaction mechanism of these gasotransmitters in renal failure should be conducted to enable developing new therapeutic tools to be associated with nanotechnology with significant benefits.

CRediT authorship contribution statement

Joana Claudio Pieretti: Conceptualization, Writing - review & editing. **Carolina Victoria Cruz Junho:** Conceptualization, Writing - review & editing. **Marcela Sorelli Carneiro-Ramos:** Supervision, Conceptualization, Writing - review & editing. **Amedea Barozzi Seabra:** Supervision, Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We have appreciated the support from FAPESP (2018/08194-2, 2018/02832-7, 2018/03089-6, 2018/03089-6, 2015/19107-5), CNPq (404815/2018-9, 313117/2019-5). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoalde Nível Superior - Brasil (CAPES) - Finance Code 001. We would like to thank GoodDeal for revising our manuscript text.

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