Review Article

Role of Hydrogen Sulfide in Ischemia-Reperfusion Injury

Dongdong Wu,1 Jun Wang,1 Hui Li,1 Mengzhou Xue,2 Ailing Ji,1 and Yanzhang Li1

1Medical College of Henan University, Kaifeng, Henan 475004, China
2Department of Neurology, Institute of Neurological Disorders, The First Affiliated Hospital of Henan University, Kaifeng 475001, China

Correspondence should be addressed to Mengzhou Xue; menzhouxue@gmail.com, Ailing Ji; ailingji@163.com, and Yanzhang Li; yanzhang206@163.com

Received 17 October 2014; Revised 10 December 2014; Accepted 10 December 2014

Academic Editor: Guangdong Yang

Copyright © 2015 Dongdong Wu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Ischemia-reperfusion (I/R) injury is one of the major causes of high morbidity, disability, and mortality in the world. I/R injury remains a complicated and unresolved situation in clinical practice, especially in the field of solid organ transplantation. Hydrogen sulfide (H2S) is the third gaseous signaling molecule and plays a broad range of physiological and pathophysiological roles in mammals. H2S could protect against I/R injury in many organs and tissues, such as heart, liver, kidney, intestine, stomach, hind-limb, lung, and retina. The goal of this review is to highlight recent findings regarding the role of H2S in I/R injury. In this review, we present the production and metabolism of H2S and further discuss the effect and mechanism of H2S in I/R injury.

1. Introduction

Ischemia-reperfusion (I/R) is a well-recognized pathological condition that is characterized by an initial deprivation of blood supply to an area or organ followed by subsequent vascular restoration and concomitant reoxygenation of downstream tissue [1]. I/R can develop as a consequence of trauma, hypertension, shock, sepsis, organ transplantation, or bypass surgery leading to end-organ failure such as acute renal tubular necrosis, bowel infarct, and liver failure. I/R can also occur under various complications of vascular diseases such as stroke and myocardial infarction [1, 2]. Several pathophysiologic mechanisms have been proposed as mediators of the damage induced by I/R, such as activation of the complement system and leukocyte recruitment, endoplasmic reticulum stress, calcium overload, reduction of oxidative phosphorylation, increased free radical concentration, development of the no-reflow phenomenon, endothelial dysfunction, and activation of signaling pathways of apoptosis, necrosis, and/or autophagy [1, 3]. Many studies have shown that there are three time frames in the protection against I/R injury: before the index ischemic episode (ischemic preconditioning), during ischemia (ischemic conditioning), and at the onset of reperfusion (ischemic postconditioning) [4, 5]. Currently, several therapeutic gases have been shown to play a role in the treatment of I/R injury, including hydrogen, nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H2S) [6].

H2S is a colorless, flammable, and water-soluble gas with the characteristic smell of rotten eggs. In the past several centuries, H2S had been known only for its toxicity and environmental hazards [7, 8]. It elicits its toxic effects by reversibly inhibiting cytochrome c oxidase (CcO), preventing oxidative phosphorylation and lowering the production of adenosine triphosphate (ATP). Recently, there has been growing evidence that H2S plays a broad range of physiological and pathophysiological functions [9, 10], including induction of angiogenesis [11], regulation of neuronal activity [9], vascular relaxation [12], glucose homeostatic regulation [13], and protection against I/R injury in heart, liver, kidney, lung, and brain [14–18]. The abnormal metabolism of H2S could result in an array of pathological disturbances in the form of hypertension, diabetes, atherosclerosis, heart failure, sepsis, inflammation, erectile dysfunction, cataracts, asthma, and neurodegenerative diseases [10]. In addition, H2S can also interact with other specific molecules, including NO [19], CcO [20], catalase [21], myoglobin [21, 22], hemoglobin [21, 22], Kelch-like ECH-associated protein 1 (Keap1) [23], cysteine residues on ATP-sensitive potassium (KATP) channels [24], epidermal growth factor receptor [25], and vascular...
endothelial growth factor receptor 2 [25, 26]. Considering H2S is involved in numerous biological processes, it is now widely accepted that H2S functions as the third signaling gasotransmitter, along with NO and CO [9].

With the deepening of research on H2S and I/R injury, the role that H2S plays in attenuating I/R injury has begun to be elucidated. In this review, we highlight recent studies that provide new insight into the production and metabolism of H2S and discuss the role and mechanism of H2S on I/R injury.

2. Production and Metabolism of H2S

2.1. Endogenous Production of H2S. H2S is endogenously generated in mammalian cells via both enzymatic and nonenzymatic pathways, although the nonenzymatic pathway is less important in H2S production [27]. With regard to the enzymatic pathway, cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) are two pyridoxal-5'-phosphate-(PLP-) dependent enzymes, which use either L-cysteine or L-cysteine together with homocysteine as their principal substrates to produce H2S [9]. Unlike CBS and CSE, 3-mercaptoppyruvate sulfurtransferase (3-MST) is a PLP-independent enzyme, which uses 3-mercapto pyruvate (3MP) as a substrate to produce H2S. 3MP is a metabolite of L-cysteine and α-ketoglutarate by cysteine aminotransferase (CAT) [9]. CSE and CBS are cytosolic enzymes with tissue-specific distributions. CBS is predominantly expressed in the central nervous system and is also found in liver, kidney, ileum, uterus, placenta, and pancreatic islets. CSE is abundant in heart, liver, kidney, uterus, ileum, placenta, and vascular smooth muscle. CSE is the most relevant H2S-producing enzyme in the cardiovascular system [9, 27]. CAT and 3-MST are localized both in cytosol and mitochondria, but the majority of these two enzymes are present in the mitochondria [9]. They have been found in the heart, kidney, liver, lung, thymus, testis, brain, and thoracic aorta and are apparently important for H2S production in the brain and vasculature [9, 27, 28]. Furthermore, a recent study has demonstrated that D-cysteine (a negative control of L-cysteine) can be metabolized to achiral 3MP by D-amino acid oxidase and can be used as a substrate for 3-MST to produce H2S in both kidney and brain [29]. During the enzymatic pathway, H2S can be immediately released or stored in a form of bound or acid-labile sulfur in the cells [30].

Apart from enzymatic pathway, endogenous H2S can also be produced through nonenzymatic processes that are less well understood [27, 30, 31]. Nonenzymatic production of H2S occurs through glucose, inorganic, and organic polysulfides (present in garlic), glutathione, and elemental sulfur [30, 31]. H2S can be generated from glucose either via glycolysis (>90%) or from phosphogluconate via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (<10%) [7, 27, 30]. Glucose could react with cysteine, methionine, or homocysteine to produce gaseous sulfur compounds such as H2S and methanethiol [7, 8, 30]. H2S is also produced through direct reduction of glutathione and elemental sulfur. Reduction of elemental sulfur to H2S is mediated through reducing equivalents of the glucose oxidation pathways such as nicotinamide adenine dinucleotide and NADPH [7, 8]. Thiosulfate is an intermediate of sulfur metabolism from cysteine and H2S formation from thiosulfate through a reductive reaction involving pyruvate, which acts as a hydrogen donor [7, 8, 32, 33]. In addition, garlic and garlic-derived organic polysulfides could induce H2S production in a thiol-dependent manner, such as diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), and S-allyl cysteine (SAC) [30–34].

2.2. Exogenous Source of H2S. H2S gas has been considered as the authentic resource of exogenous H2S [35]. Recent studies have shown that H2S gas plays important roles in promoting angiogenesis [11], ameliorating type II diabetes [13], and protecting against myocardial I/R injury [36]. However, H2S gas is not an ideal resource due to a possible toxic impact of H2S excess and difficulty in obtaining precisely controlled concentration [35]. Currently, a number of H2S-releasing compounds have already been successfully designed and developed. These compounds could be mainly divided into two types, including the “H2S donors,” which release H2S as the only mechanism of action, and the “H2S-releasing hybrid drugs,” also known as “dirty drugs” in which H2S release is an ancillary property which accompanies a principal mechanism of the hybrid drugs [35]. Inorganic sulfide salts, such as sodium hydrosulfide (NaHS), sodium sulfide (Na2S), and calcium sulfide, have been widely used as H2S donors [7, 8, 35]. As the maximum concentration of H2S released from these salts can be reached within seconds, they have been called fast-releasing H2S donors [35]. However, the effective residence time of these donors in tissues may be very short because H2S is highly volatile in solutions [35]. Ideal H2S donors for therapeutic purposes should generate H2S with relatively slow-releasing rates and longer periods of treating time. Recently, many slow-releasing H2S donors (Table 1) and H2S-releasing hybrid drugs (Table 2) have been designed and synthesized to increase the treatment efficacy of H2S.

2.3. Metabolism of H2S. In order to maintain a proper physiological balance of its metabolism, H2S can be broken down through several enzymatic and nonenzymatic processes [7, 10, 37]. The main pathway of H2S catabolism occurs in mitochondria. Mitochondrial oxidative modification converts H2S into thiosulfate through several enzymes including quinone oxidoreductase, S-dioxygenase, and S-transferase. Thiosulfate could be further converted into sulfite, which is catalyzed by thiosulfate:cyanide sulfurtransferase. Sulfitic is then rapidly oxidized to sulfate by sulfite oxidase. Therefore, sulfate is a major end-product of H2S metabolism under physiological conditions [7, 10, 37, 38]. The secondary mechanism of H2S catabolism is the methylation to methanethiol and dimethylsulfide via thiol S-methyltransferase in the cytosol [10, 37, 38]. The third pathway of H2S metabolism is the interaction of H2S with methemoglobin that leads to sulhemoglobin, which is considered as a possible biomarker of plasma H2S [10, 37, 38]. These three pathways are considered the main processes of H2S catabolism in mammals. Furthermore, recent studies have shown that H2S could be converted into sulfite via minor oxidative routes in activated neutrophils [10, 37].
| Compounds                  | H$_2$S release mechanisms | Therapeutic effects                                                                 | References |
|---------------------------|---------------------------|-------------------------------------------------------------------------------------|------------|
| GYY4137                   | Hydrolysis                | Vasodilation                                                                        | [86]       |
|                           |                           | Anti-inflammation                                                                   | [19]       |
|                           |                           | Anticancer                                                                          | [87]       |
|                           |                           | Protection of mitochondrial function                                               | [88]       |
|                           |                           | Regulation of oviductal embryo transport and myometrial contractility                | [89, 90]   |
|                           |                           | Anti-thrombotic                                                                     | [91]       |
| ADT                       | Metabolized by carboxylesterases | Neuroprotection against oxidative stress                                           | [92]       |
|                           |                           | Protection of blood-brain barrier integrity                                         | [55]       |
| ADT-OH                    | Metabolized by carboxylesterases | Neuroprotection against oxidative stress                                           | [92]       |
|                           |                           | Vasorelaxation                                                                       | [93]       |
|                           |                           | Antineuroinflammation                                                                | [94]       |
| AP39                      | Metabolized by carboxylesterases | Protection against oxidative mitochondrial DNA damage                             | [95]       |
| S-Aroylhiooximes          | Hydrolysis                | Unknown                                                                             | [96]       |
| S-Propargyl-cysteine      | Hydrolysis                | Angiogenesis promotion                                                               | [97]       |
|                           |                           | Anticancer                                                                          | [98]       |
|                           |                           | Cardioprotection                                                                     | [99]       |
|                           |                           | Anti-inflammatory                                                                    | [100]      |
| SG-1002                   | Activation after oral administration | Cardioprotection                                                                   | [101]      |
| 4-Hydroxythiobenzamide    | Hydrolysis                | Improvement of wound healing                                                         | [102]      |
| Arylthioamides            | Thiol activation          | Unknown                                                                             | [103]      |
| N-(benzoylthio)benzamides | Hydrolysis                | Unknown                                                                             | [104]      |
| S-Propyl cysteine         | Hydrolysis                | Cardioprotection                                                                     | [99]       |
| N-Acetylcysteine          | Hydrolysis                | Protection against oxidative stress                                                 | [105]      |
| N-Acetylcysteine ethyl ester | Hydrolysis                | Protection against oxidative stress                                                 | [105]      |
| SAC$^*$                   | Hydrolysis                | Protection against oxidative stress                                                 | [99]       |
| PhNCS                     | Thiol activation          | Unknown                                                                             | [106]      |
| PhNCS-COOH                | Thiol activation          | Unknown                                                                             | [106]      |
| Lawesson’s reagent        | Hydrolysis                | Anti-inflammation                                                                    | [107]      |
|                           |                           | Protection against gastric damage                                                   | [108]      |
| Dithioperoxyanhydrides    | Thiol activation          | Vasorelaxation                                                                       | [35]       |
| Thioglycine               | Bicarbonate activation    | Unknown                                                                             | [109]      |
| L-Thiovaline              | Bicarbonate activation    | Unknown                                                                             | [109]      |
| Thioamino acids           | Bicarbonate activation    | Vasorelaxation                                                                       | [109]      |
| Phosphorodithioates       | Hydrolysis                | Protection against oxidative stress                                                 | [35]       |
| S-SH compounds            | Thiol activation          | Myocardial I/R protection                                                           | [110]      |
| N-(acylthio)-benzamides   | Thiol activation          | Unknown                                                                             | [104]      |
| H$_2$S photo-donor 5      | Light activation          | Unknown                                                                             | [111]      |
| gem-Dithiol compounds     | Light activation          | Unknown                                                                             | [35]       |
| Allyl isothiocyanate      | Thiol activation          | Unknown                                                                             | [112]      |
| Benzyl isothiocyanate     | Thiol activation          | Unknown                                                                             | [112]      |
| 4-Hydroxybenzyl isothiocyanate | Thiol activation          | Unknown                                                                             | [112]      |
| Ercuin                    | Thiol activation          | Unknown                                                                             | [112]      |
| Sinigrin                  | Hydrolysis                | Unknown                                                                             | [112]      |
| Poly(ethylene glycol)-ADT | Metabolized by carboxylesterases | Protection against ischemic neuronal death                                     | [113]      |
| S-memantine               | Thiol activation          | Protection against oxidative stress                                                 | [114]      |
| ACSI                      | Metabolized by carboxylesterases | Neuroprotection                                                                   | [115]      |
|                           |                           | Anticancer                                                                           | [116]      |

$^*$This compound is also a derivative of garlic.
| Compounds   | Parent drugs | Therapeutic effects                      | References |
|-------------|--------------|------------------------------------------|------------|
| ACS2        | Valproic acid| Anticancer, Antiangiogenesis              | [116, 117] |
| ACS6        | Sildenafil   | Proerectile, Neuroprotection, Protection against oxidative stress | [118, 119, 120] |
| ACS14       | Aspirin      | Protection against oxidative stress, Prevent the progression of atherosclerosis, Antiaggregatory, Protection against I/R injury, Modulation of thiol homeostasis, Neuroprotection | [121, 122, 123, 124, 125, 115] |
| ACS15*      | Diclofenac   | Anticancer, Antiosteolysis, Anti-inflammation, Antiangiogenesis | [126, 127, 128, 117] |
| ACS18       | Sulindac     | Anticancer, Antiangiogenesis              | [126, 117] |
| ACS21       | Salicylic acid| Protection against I/R injury            | [124]      |
| ACS32       | Diclofenac   | Antiosteolysis                           | [127]      |
| ACS33       | Valproic acid| Anticancer, Inhibition of histone deacetylase activity | [129]      |
| ACS67       | Latanoprost  | Regulation of insulin secretion, Neuroprotection | [114, 85]  |
| ACS83       | L-DOPA       | Anti-inflammation                         | [130]      |
| ACS84       | L-DOPA       | Anti-inflammation, Neuroprotection        | [131, 132] |
| ACS85       | L-DOPA       | Anti-inflammation                         | [118]      |
| ACS86       | L-DOPA       | Anti-inflammation                         | [118]      |
| ATB-284     | Unknown      | Prevention against irritable bowel syndrome | [133]      |
| ATB-337*    | Diclofenac   | Anti-inflammation                         | [134]      |
| ATB-343     | Indomethacin | Anti-inflammation                         | [135]      |
| ATB-345     | Naproxen     | Anti-inflammation                         | [136]      |
| ATB-346     | Naproxen     | Anti-inflammation, Anticancer             | [136, 137] |
| ATB-429     | Mesalamine   | Anti-inflammation, Abirritation           | [138, 139] |
| HS-aspirin (HS-ASA) | Aspirin | Anticancer                                | [140]      |
| Compound 8e | 3-n-Butylphthalide | Antithrombosis                           | [141]      |
| H2S-EXP 3174| Active metabolite of losartan | Vasorelaxation                           | [142]      |
| NOSH-aspirin (NBS-1120) | Aspirin | Anticancer                                | [143]      |
| NOSH-naproxen (AVT-219) | Naproxen | Anti-inflammation                         | [144]      |
| NOSH-sulindac (AVT-18A) | Sulindac | Anti-inflammation                         | [145]      |
| S-diclofenac* | Diclofenac | Anti-inflammation, Protection against I/R injury | [146]      |
| S-zofenopril | Zofenopril   | Improvement of vascular function          | [147]      |

*These compounds are remarkably similar to each other.
3. H$_2$S and I/R Injury

3.1. H$_2$S and Myocardial I/R Injury. Myocardial ischemia is a common clinical symptom characterized by low pH values, low oxygen, and high extracellular potassium concentration, which may cause arrhythmias, cardiac dysfunction, myocardial infarction, and sudden death [3, 5, 6]. The damaged myocardial structure and decreased heart function induced by ischemia can be repaired with subsequent reperfusion. The effectiveness of reperfusion depends on the duration and severity of prior ischemia [6, 39]. However, myocardial reperfusion could also activate a complex inflammatory response, which may finally lead to myocardial ischemia/reperfusion injury (MI/R), such as arrhythmias, myocardial stunning, microvascular dysfunction, and myocyte death [2, 40]. Therefore, it is necessary to develop effective cardioprotective strategies and agents against MI/R to improve myocardial function and to reduce the risk of cardiovascular events [4].

H$_2$S is now considered as an endogenous signaling molecule which plays an important role in the cardiovascular system [6, 15, 27]. In the heart, H$_2$S is produced in the fibroblasts, myocardium, and blood vessels from L-cysteine by CSE, CBS, and 3-MST and accumulates at relatively high local concentrations [6, 27, 30]. An accumulating body of evidence indicates that exogenous or endogenous H$_2$S could exert cardioprotection against MI/R in cardiac myocytes, isolated hearts, and intact animals. However, it is currently difficult to define the precise underlying mechanisms for this protection. A summary of what is known about the mechanisms by which H$_2$S and its donors-induced cardioprotection against MI/R is shown in Table 3.

3.2. H$_2$S and Hepatic I/R Injury. Liver I/R-induced injury represents a continuum of organic processes that could produce profound liver damage and ultimately lead to morbidity and mortality [41, 42]. Hepatic I/R injury has now been considered a worldwide health problem and usually occurs in liver transplantation, hemorrhagic shock and resuscitation, trauma, liver resection surgery, and aortic injury during abdominal surgery [41–43]. Hepatic I/R injury can be categorized into warm I/R and cold storage reperfusion injury, which share a common mechanism in the disease aetiology [41, 42]. Increasing number of experimental and clinical studies indicate that pathways/factors involved in the hepatic I/R injury include liver Kupffer cells and neutrophils, intracellular calcium overload, oxidative stress, anaerobic metabolism, mitochondria, adhesion molecules, chemokines, and proinflammatory cytokines [41, 42, 44, 45]. Despite significant advances in surgical techniques and perioperative cares, hepatic I/R injury remains one of the major complications in hepatic resection and transplantation [46]. Novel agents/drugs exhibiting antioxidative, anti-inflammatory, and cytoprotective activities may be possible candidates for protecting the liver from I/R injury [46]. Recent studies have shown that H$_2$S could significantly attenuate hepatic I/R injury in several ways, including inflammation, apoptosis, oxidation, and AKT activation (Table 4). The results suggest that H$_2$S has a protective effect against hepatic I/R injury, and targeting H$_2$S may present a promising approach against I/R-induced liver injury.

3.3. H$_2$S and Renal I/R Injury. Acute kidney injury (AKI) is a common and serious complication of critical illness and is associated with high morbidity, mortality, and resource utilization [25, 47, 48]. Renal I/R injury is one of the leading causes of AKI in many clinical settings [47, 48]. Renal I/R injury often arises from shock and various surgical procedures such as kidney transplantation and resection [47–49]. H$_2$S plays important physiological and pathological roles in the kidney [48]. For instance, it participates in the control of renal function and increases urinary sodium excretion via both tubular and vascular actions in the kidney [50].

CSE deficiency in mice could lead to reduced renal H$_2$S production and increase severity of damage and mortality after renal I/R injury, which indicates that H$_2$S may play a role in alleviating renal I/R injury [14]. More recently, there is growing evidence regarding the beneficial effects of H$_2$S on ameliorating renal I/R injury mainly via a variety of antioxidant, antiapoptotic, and anti-inflammatory effects (Table 5). These studies indicate that H$_2$S and its donors may be of benefit in conditions associated with renal I/R injury, such as renal transplantation.

3.4. H$_2$S and Cerebral I/R Injury. Ischemic cerebrovascular disease is one of the most common disorders that greatly threaten human health with high morbidity, disability, and mortality [51]. Cerebral I/R injury is mainly characterized by a deterioration of ischemic but potentially salvageable brain tissue of an ischemic injury after reperfusion [52, 53]. There are a number of risk factors involved in cerebral I/R injury, such as excitotoxicity, mitochondrial dysfunction, formation of free radicals, breakdown of the blood-brain barrier (BBB), edema, neuroinflammation, and apoptosis [52–54]. Emerging evidences indicate that H$_2$S functions not only as a neuromodulator, but also as a neuroprotectant in the central nervous system [18, 55–57]. In an in vivo model of cerebral I/R injury, treatment with low concentration of H$_2$S decreased the infarct size and improved the neurological function via antiapoptotic effect, implying that H$_2$S has a therapeutic role in cerebral ischemic stroke [18, 57]. DAS, an H$_2$S donor, could also protect the brain from I/R injury partly via its antiapoptotic effects [58]. ADT, another H$_2$S donor, decreased the infarct size and protected BBB integrity by suppressing local inflammation and nicotinamide adenine dinucleotide phosphate oxide 4-derived ROS generation [55]. However, it is notable that the effects of H$_2$S on cerebral I/R injury are controversial [56]. Treatment with a higher dose of exogenous H$_2$S donor could deteriorate the effects of cerebral I/R injury [18, 59]. These opposite effects of H$_2$S on cerebral I/R injury may be partially associated with the concentration of H$_2$S in brain. This research offers a novel insight for future studies on the cytoprotective effects of a proper dose of H$_2$S on central nervous system degenerative diseases, such as Alzheimer's disease and Parkinson's disease.

3.5. H$_2$S and Intestinal I/R Injury. Intestinal I/R injury is considered to be a major and frequent problem in many clinical conditions, including intestinal mechanical obstruction, abdominal aortic aneurysm surgery, cardiopulmonary...
Table 3: Effects of H₂S and its donors in myocardial I/R injury.

| Experimental models                      | Effects                                                                 | Proposed mechanisms                                                                 | References |
|------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------|
| Myocardial I/R in vivo (rat)             | NaHS (0.2 mg/kg, prior to R) protects against the effects of haemorrhage-induced I/R | Upregulation of the protein kinase B/endothelial nitric oxide synthase pathway     | [148]     |
| Regional myocardial I/R in vivo (rat)    | NaHS (3 mg/kg, 15 min prior to I) shows cardioprotective effects       | Combination of antiapoptotic and anti-inflammatory effects                           | [149]     |
| Isolated perfused heart ex vivo (rat)    | NaHS (100 μM, plus histidine buffer solution, prior to R) enhances cardiac performance | Prevention of apoptosis and preservation of the phosphorylative system              | [150]     |
| Isolated perfused heart ex vivo (rat)    | NaHS (0.1–100 μM, at the onset of R) protects rat heart against I/R injury | Mitochondrial K<sub>ATP</sub> channel opening                                       | [151]     |
| Primary cultured neonatal cardiomyocytes (rat) | NaHS (25–200 μM, 30 min prior to H) protects cardiomyocytes from oxidative stress | Inhibition of mitochondrial complex IV and enhancement of SOD activity              | [152]     |
| Isolated perfused heart ex vivo (rat)    | NaHS (10 μM, at the onset of R) protects isolated rat hearts from I/R injury | Activation of the Janus kinase 2/signal transducer and activator of transcription 3 signaling pathway | [153]     |
| Isolated perfused heart ex vivo (rat)    | NaHS (40 μM, throughout the experiment) provides myocardial protection | Possibly activation of the expression of heat shock protein 72                     | [154]     |
| Isolated perfused heart ex vivo (rat)    | L-cysteine (0.1–10 mM, 10 min before I until 10 min after R) induces limitation of infarct size | Dependent on H₂S synthesis                                                         | [155]     |
| Myocardial I/R in vivo (rat)             | NaHS (14 μM/kg, 7 days before myocardial I/R) significantly reduces the myocardial infarct size | Antiapoptotic, antioxidative, and anti-inflammatory activities                      | [156]     |
| Isolated perfused heart ex vivo (rat)    | NaHS (100 μM, prior to I) significantly decreases the duration and severity of I/R-induced arrhythmias | Mitochondrial K<sub>ATP</sub> channel opening                                       | [157]     |
| Isolated perfused heart ex vivo (rat)    | NaHS (100 μM, prior to I) significantly decreases myocardial infarct size and improves heart contractile function | Activation of K<sub>ATP</sub>/PKC/ERK1/2 and PI3K/Akt pathways                     | [158]     |
| Isolated cardiac myocytes (rat)          | NaHS (100 μM, prior to I) increases cell viability, percentage of rod-shaped cells, and myocyte contractility | K<sub>ATP</sub>/PKC dependent induction of COX-2 expression and nitric oxide-induced COX-2 activation | [159]     |
| Myocardial I/R in vivo (mice)            | H₂S (100 ppm, prior to I) has protective properties in I/R injury       | Reduction of myocardial ROS production and the inhibition of inflammation, necrosis, and fibrogenesis | [36]      |
| Regional myocardial I/R in vivo (pig)    | Na₂S (100 μg/kg bolus + 1 mg/kg/hr infusion, 10 min prior to R) improves myocardial function and reduces infarct size | Anti-inflammatory properties                                                       | [160]     |
| Regional myocardial I/R in vivo (pig)    | Na₂S (100 μg/kg bolus + 1 mg/kg/hr infusion, throughout the experiment) reduces myocardial infarct size | Antiapoptotic activities                                                          | [161]     |
| Regional myocardial I/R in vivo (rat)    | NaHS (0.1–10 μM, 10 min prior to I until 10 min into R) results in a concentration-dependent limitation of infarct size | Mitochondrial K<sub>ATP</sub> channel opening                                       | [162]     |
| Myocardial I/R in vivo (rat)             | NaHS (0.2 mg/kg, prior to R) protects against the effects of haemorrhage-induced I/R | Protection against oxidative stress                                               | [163]     |
| Primary cultured neonatal cardiomyocytes (rat) | NaHS (1–100 μM, 30 min prior to H) shows concentration-dependent inhibitory effects on cardiomyocyte apoptosis induced by H/R | Induction of phosphorylation of GSK-3 and inhibition of mitochondrial permeability transition pore opening | [164]     |
| Myocardial I/R in vivo (mice)            | Na₂S (0.1 mg/kg, 7 days prior to I) attenuates myocardial I/R injury    | Activation of nuclear factor erythroid-2-related factor-2 signaling in an Erk-dependent manner | [165]     |
studies have shown that H\textsubscript{2}S agents/drugs for the treatment of intestinal I/R injury. Recent [61, 63]. Therefore, it is urgent to develop new therapeutic treatments have been applied to clinical research, the mortality induced by intestinal I/R injury remains very high [62, 63]. Although many advanced dysfunctions syndrome [61, 63]. There is a number of clinical conditions contribute to gastric I/R injury, including peptic ulcer bleeding, vascular rupture or surgery, ischemia gastrointestinal disease, and hemorrhagic shock [66]. However, there are few satisfactory clinical methods in the treatment of gastric I/R injury [67]. H\textsubscript{2}S has been found to play an important role in protecting against gastric I/R injury. Endogenous H\textsubscript{2}S had a protective effect against gastric I/R in rats by enhancing the antioxidant capacity through increasing the contents of GSH and SOD [68]. Another study has shown that NaHS and L-cysteine could protect the gastric mucosa against I/R damage mainly mediated by altering mRNA expression and

| Experimental models | Effects | Proposed mechanisms | References |
|---------------------|---------|---------------------|------------|
| Myocardial I/R in vivo (rat) | NaHS (14 μM/kg, 7 days prior to I) inhibits apoptosis of cardiomyocytes induced by myocardial I/R | Enhancement of the phosphorylation of apoptosis repressor with caspase recruitment domain | [166] |
| Myocardial I/R in vivo (mice) | Na\textsubscript{2}S (10–500 μg/kg, prior to R) limits infarct size and preserves left ventricular function | Inhibition of myocardial inflammation and preservation of both mitochondrial structure and function | [167] |
| Myocardial I/R in vivo (mice) | Na\textsubscript{2}S (100 μg/kg, 1h prior to I) reduces myocardial infarct size | miR-21-dependent attenuation of ischemic and inflammatory injury | [168] |
| Myocardial I/R in vivo (mice) | Na\textsubscript{2}S (100 μg/kg, 24 h prior to I) reduces myocardial infarct size | Combination of antioxidant and antiapoptotic signaling | [169] |
| Isolated perfused heart ex vivo (rabbit) | Allitridum (60 μM, prior to I) reduces myocardial infarct size | Activation of PKC | [170] |
| Myocardial I/R in vivo (mice) | DATS (200 μM/kg, prior to R) significantly reduces infarct size and increases myocardial contractile function | Preservation of endogenous hydrogen sulfide and increase of nitric oxide bioavailability | [32] |
| Myocardial I/R in vivo (mice) | Na\textsubscript{2}S (100 μg/kg, prior to R) protects against the structural and functional deterioration of the left ventricle | Protection against oxidative stress and mitochondrial dysfunction | [15] |
| Isolated perfused heart ex vivo (rat) | NaHS (50 μM, prior or post to I) protects against cardiac I/R injury | Phosphorylation of mammalian target of rapamycin C2 | [171] |
| Myocardial I/R in vivo (rat) | NaHS (3 mg/kg, 15 min prior to I) significantly reduces myocardial infarct size | Mitochondrial K\textsubscript{ATP} channel opening | [172] |
| Primary cultured neonatal cardiomyocytes (rat) | NaHS (30 μM, 30 min prior to H) attenuates cardiomyocyte apoptosis and enhances cell viability | Protection of cardiomyocytes against I/R-induced apoptosis by stimulating Bcl-2 | [173] |
| Isolated perfused heart ex vivo (mice) | Na\textsubscript{2}S (10 μM, 40 seconds after the start of R) markedly improves the recovery of myocardial function | Nitric oxide synthase 3-dependent signaling pathway | [174] |
| Myocardial I/R in vivo (rat) | NaHS (14 μM/kg/d, 6 d prior to I) markedly reduces heart infarct size and has great improvement in blood pressure | Upregulation of survivin | [175] |
| Myocardial I/R in vivo (pig) | Na\textsubscript{2}S (0.2 mg/kg, prior to R) markedly reduces myocardial infarct size and improves regional left ventricular function | Higher expression of phospho-GSK-3β and lower expression of apoptosis-inducing factor | [176] |

H/R: hypoxia/reoxygenation; SOD: superoxide dismutase; PKC: protein kinase C; ERK1/2: extracellular signal regulated kinase 1/2; PI3K (PtdIns3K): phosphatidylinositol3-kinase; Akt (PKB): protein kinase B; COX-2: cyclooxygenase-2; ROS: reactive oxygen species; GSK-3: glycogen synthase kinase-3.

H\textsubscript{2}S and Gastric I/R Injury. Gastric I/R injury is an important and common clinical problem which could lead to mucosal injury [66]. A number of clinical conditions contribute to gastric I/R injury, including peptic ulcer bleeding, vascular rupture or surgery, ischemia gastrointestinal disease, and hemorrhagic shock [66]. However, there are few satisfactory clinical methods in the treatment of gastric I/R injury [67]. H\textsubscript{2}S has been found to play an important role in protecting against gastric I/R injury. Endogenous H\textsubscript{2}S had a protective effect against gastric I/R in rats by enhancing the antioxidant capacity through increasing the contents of GSH and SOD [68]. Another study has shown that NaHS and L-cysteine could protect the gastric mucosa against I/R damage mainly mediated by altering mRNA expression and

bypass, strangulated hernias, liver and intestinal transplantation, mesenteric artery occlusion, shock, and severe trauma [60–64]. This injury can lead to the development of systemic inflammatory response syndrome and multiple organ dysfunction syndrome [62, 63]. Although many advanced treatments have been applied to clinical research, the mortality induced by intestinal I/R injury remains very high [61, 63]. Therefore, it is urgent to develop new therapeutic agents/drugs for the treatment of intestinal I/R injury. Recent studies have shown that H\textsubscript{2}S has anti-ischemic activity in the intestinal I/R model. NaHS could significantly reduce the severity of intestinal I/R injury and dramatically increase the activities of SOD and glutathione peroxidase (GSH-Px) in both serum and intestinal tissue, which suggests that H\textsubscript{2}S protects against intestinal I/R injury by increasing the levels of antioxidant enzymes [63]. In addition, administration of NaHS after the onset of ischemia can attenuate I/R-induced damage of intestinal tissues both in vitro and in vivo [65]. These observations provide new insight regarding the potential use of H\textsubscript{2}S as a therapeutic agent to limit intestinal I/R injury. 3.6. H\textsubscript{2}S and Gastric I/R Injury. Gastric I/R injury is an important and common clinical problem which could lead to mucosal injury [66]. A number of clinical conditions contribute to gastric I/R injury, including peptic ulcer bleeding, vascular rupture or surgery, ischemia gastrointestinal disease, and hemorrhagic shock [66]. However, there are few satisfactory clinical methods in the treatment of gastric I/R injury [67]. H\textsubscript{2}S has been found to play an important role in protecting against gastric I/R injury. Endogenous H\textsubscript{2}S had a protective effect against gastric I/R in rats by enhancing the antioxidant capacity through increasing the contents of GSH and SOD [68]. Another study has shown that NaHS and L-cysteine could protect the gastric mucosa against I/R damage mainly mediated by altering mRNA expression and
### Table 4: Effects of H$_2$S and its donors in hepatic I/R injury.

| Experimental models | Effects | Proposed mechanisms | References |
|---------------------|---------|---------------------|------------|
| Hepatic I/R *in vivo* (rat) | NaHS (28 μM/kg, prior to R) attenuates the injured hepatic function and the synthetic action of hepatocytes | Inhibition of lipid peroxidation and inflammation reactions | [177] |
| Hepatic I/R *in vivo* (mice) | NaHS (1.5 mg/kg, 1 h prior to I) protects against hepatic I/R injuries | Activation of the PtdIns3K-AKT1 pathway | [17] |
| Hepatic I/R *in vivo* (rat) | NaHS (14 μM/kg, 30 min prior to I) significantly attenuates the severity of liver injury and inhibits the production of lipid peroxidation | Antioxidant and antiapoptotic activities | [46] |
| Hepatic I/R *in vivo* (rat) | DAS (1.75 mM/kg, 12–15 h prior to I) protects the liver from warm I/R injury | Induction of heme oxygenase-1 and inhibition of cytochrome P450 2E1 | [178] |
| Hepatic I/R *in vivo* (mice) | Na$_2$S (1 mg/kg, 5 min prior to R) protects the murine liver against I/R injury | Upregulation of intracellular antioxidant and antiapoptotic signaling pathways | [179] |
| Hepatic I/R *in vivo* (mice) | H$_2$S (100 ppm, 5 min prior to R) protects the liver against I/R injury | Reduction of necrosis, apoptosis, and inflammation | [180] |
| Hepatic I/R *in vivo* (mice) | NaHS (14 and 28 μM/kg, 30 min prior to I) attenuates hepatic I/R injury | Weaken the apoptosis through the inhibition of c-Jun N-terminal protein kinase 1 signaling pathway | [181] |
| Hepatic I/R *in vivo* (rat) | NaHS (28 μM/kg, prior to R) attenuates hepatic I/R injury | Inhibition of mitochondrial permeability transition pore opening, reduction of cell apoptosis, and activation of Akt-GSK-3β signaling | [182] |

### Table 5: Effects of H$_2$S and its donors in renal I/R injury.

| Experimental models | Effects | Proposed mechanisms | References |
|---------------------|---------|---------------------|------------|
| Renal I/R *in vivo* (mice) | NaHS (1 mg/kg, 15 min prior to I) rescues mice from the injury and mortality | Modulation of oxidative stress | [14] |
| Renal I/R *in vivo* (mice) | H$_2$S (100 ppm, before and after treatment) shows protective effects on survival, renal function, apoptosis, and inflammation | A hypometabolic state induced by H$_2$S | [183] |
| Renal I/R *in vivo* (pig) | Na$_2$S (100 μg/kg, 10 min prior to R) results in a marked reduction in kidney injury and preserves glomerular function | Anti-inflammatory effects | [184] |
| Isolated perfused kidney *ex vivo* (pig) | H$_2$S (0.5 mM, 10 min before and after R) ameliorates the renal dysfunction | Activation of K$_{ATP}$ channels | [185] |
| Renal I/R *in vivo* (mice) | NaHS (100 μM/kg, 30 min prior to I) significantly attenuates I/R injury-induced renal dysfunction | The increase in expression of CSE | [186] |
| Renal I/R *in vivo* (rat) | NaHS (100 μM/kg, 15 min prior to I and 5 min prior to R) attenuates renal I/R injury | Antiapoptotic and anti-inflammatory effects | [187] |
| Warm renal I/R *in vivo* (rat) | NaHS (150 μM, at time of renal pedicle clamping and during R) improves long-term renal function and decreases long-term inflammation | Antiapoptotic and anti-inflammatory effects | [188] |
| Warm renal I/R *in vivo* (rat) | NaHS (150 μM, during I and R) increases renal capillary perfusion and improves acute tubular necrosis and apoptosis | Decrease of leukocyte migration and inflammatory responses | [189] |
| Renal I/R *in vivo* (rat) | Na$_2$S (2 mg/kg, 2 h prior to I) attenuates tissue injury and organ dysfunction | Antioxidant and anti-inflammatory effects | [190] |
| Renal I/R *in vivo* (rat) | NaHS (100 μg/kg, 20 min prior to I or 10 min prior to R) protects against renal I/R injury | Antioxidant and antiapoptotic effects | [191] |
plasma release of proinflammatory cytokines [69]. Furthermore, NaHS and L-cysteine also showed gastroprotective effects against I/R injury by Keap1 s-sulhydration, nuclear factor-kappa B dependent anti-inflammation, and mitogen-activated protein kinase dependent antiapoptosis pathway [66]. Thus, H$_2$S and its donors may have potential therapeutic value in acute gastric mucosal lesion, which is often caused by I/R.

3.7. H$_2$S and Hind-Limb I/R Injury. I/R injury can occur in skeletal muscle during elective surgery (i.e., free tissue transfer) and lower extremity arterial occlusion [70, 71]. Limb I/R injury may result in a series of postreperfusion syndromes, such as crush syndrome, compartment syndrome, and myonephropathic-metabolic syndrome [72]. Currently, clinical practice mainly focuses on reducing the duration of ischemia to minimize the ischemic injury in skeletal muscle [70, 71]. Therapeutic interventions that change the biochemical environment during the ischemic and/or reperfusion period may result in amelioration of subsequent cellular damage [71]. Treatment with NaHS for 20 minutes before the onset of hind-limb ischemia or reperfusion could result in significant protection against the cellular damage induced by I/R [71, 73]. However, administration of NaHS for 1 minute before reperfusion did not show any protection against limb I/R Injury [73]. Whether H$_2$S could protect against limb I/R injury in a dose- and time-dependent manner needs further investigation.

3.8. H$_2$S and Lung I/R Injury. Lung I/R injury occurs in various clinical conditions such as lung transplantation, cardiopulmonary bypass, trauma, cardiac bypass surgery, sleeve lobectomy, shock, pulmonary embolism, resuscitation from circulatory arrest, and reexpansion pulmonary edema [16, 74–77]. Lung I/R injury is characterized by increased pulmonary vascular resistance, worsened lung compliance, poor lung oxygenation, edema, and increased pulmonary endothelial permeability [16, 78]. Currently, there is no effective therapy available for the lung I/R injury. The precise mechanism of lung I/R injury needs to be further elucidated [16, 74]. A recent study has shown that preperfusion with H$_2$S could attenuate the lung I/R injury by reducing lung oxidative stress [16], which suggests that administration of H$_2$S or its donors might be a novel preventive and therapeutic strategy for lung I/R injury.

3.9. H$_2$S and Retinal I/R Injury. Retinal I/R injury is a common clinical condition and is associated with the loss of neurons, morphological degeneration of the retina, loss of retinal function, and ultimately vision loss [79, 80]. Emerging evidence suggests that retinal I/R injury plays an important role in the pathologic processes of several ocular diseases such as diabetic retinopathy, retinopathy of prematurity, acute glaucoma, and retinal vascular occlusion [81, 82]. Retinal I/R injury often results in visual impairment and blindness because of the lack of effective treatment [81, 83]. One recent study has indicated that rapid preconditioning with inhaled H$_2$S can mediate antiapoptotic effects and thus protect the rat retina against I/R injury [84]. ACS67, a H$_2$S-releasing derivative of latanoprost acid, possesses neuroprotective properties and could attenuate retinal ischemia in vivo and decrease the oxidative insult to RGC-5 cells (retinal ganglion cells) in vitro [85]. These results suggest that H$_2$S represents a novel and promising therapeutic agent to counteract neuronal injuries in the eye [84]. Further studies are needed to prove the neuroprotective propensity of H$_2$S in retinal I/R injury using a postconditioning approach.

4. Concluding Remarks

H$_2$S is now considered as the third signaling gasotransmitter which plays a broad range of physiological and pathophysiological functions, including vascular relaxation, induction of angiogenesis, regulation of neuronal activity, and glucose homeostatic regulation. H$_2$S can be endogenously generated via both enzymatic and nonenzymatic pathways and mainly metabolized through three pathways in mammals. However, whether H$_2$S could be generated and metabolized via another pathway should be further studied and confirmed. In addition, more efforts should be made to illuminate the expressions and functions of H$_2$S-generating enzymes in different organ and tissue. In order to increase the treatment efficacy of H$_2$S, a number of slow-releasing H$_2$S donors and H$_2$S-releasing hybrid drugs have been successfully designed, synthesized, and proved to be effective in vitro, ex vivo, and in vivo. Novel synthetic strategy should be developed to extend the exposure time of H$_2$S donor. Agents/drugs with antiapoptotic, antioxidative, anti-inflammatory, and antitumor effects could be conjugated with H$_2$S donor to enhance their therapeutic effects. Furthermore, new drug targeting carrier systems should be designed to effectively transport the H$_2$S donor to the targeted organ or tissue.

I/R is a pathological condition that is characterized by an initial deprivation of blood supply to an area or organ followed by the subsequent restoration of perfusion and concomitant reoxygenation. Novel mechanisms associated with I/R need to be further studied and illuminated in addition to the existing pathophysiologic mechanisms. Increasing number of studies have shown that H$_2$S could protect against I/R injury in many organs and tissues, such as heart, liver, kidney, brain, intestine, stomach, hind-limb, lung, and retina. Whether H$_2$S could exert protection against I/R injury in other organs and/or tissues need to be further demonstrated. In addition, the molecular targets of H$_2$S in I/R injury are also needed to be clarified. Ischemic preconditioning, conditioning, and postconditioning are three time frames in the protection against I/R injury. Proper time frame and optimal duration of treatment should be confirmed according to the physicochemical property of H$_2$S-releasing compounds. Considering different doses of H$_2$S-releasing compounds may exert different therapeutic effects, proper dose range should also be further explored to obtain a better therapeutic efficacy. Currently, researches into the molecular mechanisms of H$_2$S in I/R injury using animal experiments have made some progress. Clinical evidence-based research should also be useful in further exploring the little understood field of the role of H$_2$S in I/R injury. In addition, longer-term studies are...
required to determine whether H$_2$S treatment permanently improves organ function following I/R injury and whether this effect reduces long-term morbidity and mortality.

In conclusion, with the rapid developments of design and synthetic strategies, as well as better understanding of the precise mechanisms behind the role of H$_2$S in I/R injury, treatment with H$_2$S or its donors in proper dose range and time frame will exhibit more potent therapeutic effects against I/R injury in further preclinical research and clinical application.

**Conflict of Interests**

The authors declare no conflict of interests related to this work.

**Acknowledgments**

This work was supported by Grant 132300410012 (Yanzhang Li) from Henan Provincial Science & Technology, China, and National Natural Science Foundation of China Grant 81471174 (Mengzhou Xue) and Grant 31300884 (Jun Wang). Drs. Ji, Li, and Xue are Yellow River Scholars in Biology, Biochemistry and Neurology, respectively. The authors apologize to all colleagues whose relevant contributions could not be cited due to space limitations.

**References**

[1] H. K. Eltzschig and T. Eckle, “Ischemia and reperfusion—from mechanism to translation,” Nature Medicine, vol. 17, no. 11, pp. 1391–1401, 2011.
[2] C. Duehrkop and R. Rieben, "Ischemia/reperfusion injury: effect of simultaneous inhibition of plasma cascade systems versus specific complement inhibition," Biochemical Pharmacology, vol. 88, no. 1, pp. 12–22, 2014.
[3] R. B. Jennings, "Historical perspective on the pathology of myocardial ischemia/reperfusion injury," Circulation Research, vol. 113, no. 4, pp. 428–438, 2013.
[4] D. J. Hausenloy and D. M. Yellon, “The therapeutic potential of ischemic conditioning: an update,” Nature Reviews Cardiology, vol. 8, no. 11, pp. 619–629, 2011.
[5] G. Heusch, P. Libby, B. Gersh et al., “Cardiovascular remodelling in coronary artery disease and heart failure,” The Lancet, vol. 383, no. 9932, pp. 1933–1943, 2014.
[6] I. Andreoudou, E. K. Lliodormitis, T. Rassaf, R. Schulz, A. Papapetropoulos, and P. Ferdinandy, “The role of gasotransmitters NO, H$_2$S and CO in myocardial ischaemia/reperfusion injury and cardioprotection by preconditioning, postconditioning and remote conditioning,” British Journal of Pharmacology, 2014.
[7] G. K. Kolluru, X. Shen, S. C. Bir, and C. G. Kevil, “Hydrogen sulfide chemical biology: pathophysiological roles and detection,” Nitric Oxide: Biology and Chemistry, vol. 35, pp. 5–20, 2013.
[8] Q. Li and J. R. Lancaster Jr., “Chemical foundations of hydrogen sulfide biology,” Nitric Oxide—Biology and Chemistry, vol. 35, pp. 21–34, 2013.
[9] H. Kimura, “The physiological role of hydrogen sulfide and beyond,” Nitric Oxide - Biology and Chemistry, vol. 41, pp. 4–10, 2014.
[10] A. Stein and S. M. Bailey, “Redox biology of hydrogen sulfide: implications for physiology, pathophysiology, and pharmacology,” Redox Biology, vol. 1, no. 1, pp. 32–39, 2013.
[11] A. Papapetropoulos, A. Pyrrochoua, Z. Altauyn et al., “Hydrogen sulfide is an endogenous stimulator of angiogenesis,” Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 51, pp. 21972–21977, 2009.
[12] G. Yang, L. Wu, B. Jiang et al., “H$_2$S as a physiologic vasorelaxant: hypertension in mice with deletion of cystathionine γ-lyase,” Science, vol. 322, no. 5901, pp. 587–590, 2008.
[13] R. Xue, D.-D. Hao, J.-P. Sun et al., “Hydrogen sulfide treatment promotes glucose uptake by increasing insulin receptor sensitivity and ameliorates kidney lesions in type 2 diabetes,” Antioxidants and Redox Signaling, vol. 19, no. 1, pp. 5–23, 2013.
[14] E. M. Bos, R. Wang, P. M. Snijder et al., “Cystathionine γ-lyase protects against renal ischemia/reperfusion by modulating oxidative stress,” Journal of the American Society of Nephrology, vol. 24, no. 5, pp. 759–770, 2013.
[15] J. W. Calvert, M. Elston, C. K. Nicholson et al., “Genetic and pharmacologic hydrogen sulfide therapy attenuates ischemia-induced heart failure in mice,” Circulation, vol. 122, no. 1, pp. 11–19, 2010.
[16] Z. Fu, X. Liu, B. Geng, L. Fang, and C. Tang, “Hydrogen sulfide protects rat lung from ischemia-reperfusion injury,” Life Sciences, vol. 82, no. 23–24, pp. 1196–1202, 2008.
[17] D. Wang, Y. Ma, Z. Li et al., “The role of AKT1 and autophagy in the protective effect of hydrogen sulphide against hepatic ischemia/reperfusion injury in mice,” Autophagy, vol. 8, no. 6, pp. 954–962, 2012.
[18] J. Yin, C. Tu, J. Zhao et al., “Exogenous hydrogen sulfide protects against global cerebral ischemia/reperfusion injury via its antioxidant, anti-inflammatory and anti-apoptotic effects in rats,” Brain Research, vol. 1491, pp. 188–196, 2013.
[19] M. L. Io Faro, B. Fox, J. L. Whatmore et al., “Hydrogen sulfide and nitric oxide interactions in inflammation,” Nitric Oxide, vol. 41, pp. 38–47, 2014.
[20] J. P. Collman, S. Ghosh, A. Dey, and R. A. Decr´eau, “Using a functional enzyme model to understand the chemistry behind hydrogen sulfide induced hibernation,” Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 52, pp. 22090–22095, 2009.
[21] B. B. Rios-Gonzalez, E. M. Román-Morales, R. Pietri, and J. López-Garriga, “Hydrogen sulfide activation in hemeproteins: the sulfheme scenario,” Journal of Inorganic Biochemistry, vol. 133, pp. 78–86, 2014.
[22] R. Pietri, E. Román-Morales, and J. López-Garriga, “Hydrogen sulfide and hemeproteins: knowledge and mysteries,” Antioxidants and Redox Signaling, vol. 15, no. 2, pp. 393–404, 2011.
[23] J. M. Hourihan, J. G. Kenna, and J. D. Hayes, “The gasotransmitter hydrogen sulfide induces Nrf2-target genes by inactivating the keap1 ubiquitin ligase substrate adaptor through formation of a disulfide bond between Cys-226 and Cys-613,” Antioxidants and Redox Signaling, vol. 19, no. 5, pp. 465–481, 2013.
[24] B. Jiang, G. Tang, K. Cao, L. Wu, and R. Wang, “Molecular mechanism for H$_2$S-induced activation of K$_{ATP}$ channels,” Antioxidants and Redox Signaling, vol. 12, no. 10, pp. 1167–1178, 2010.
[25] S.-N. Ge, M.-M. Zhao, D.-D. Wu et al., “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,”
**Antioxidants & Redox Signaling**, vol. 21, no. 15, pp. 2061–2082, 2014.

[26] B.-B. Tao, S.-Y. Liu, C.-C. Zhang et al., “VEGFR2 functions as an H2S-targeting receptor protein kinase with its novel Cys1045-Cys1024 disulfide bond serving as a specific molecular switch for hydrogen sulfide actions in vascular endothelial cells,” *Antioxidants and Redox Signaling*, vol. 19, no. 5, pp. 448–464, 2013.

[27] D. J. Polhemus and D. J. Lefer, “Emergence of hydrogen sulfide as an endogenous gaseous signaling molecule in cardiovascular disease,” *Circulation Research*, vol. 114, no. 4, pp. 730–737, 2014.

[28] N. Shibuya, Y. Mikami, Y. Kimura, N. Nagahara, and H. Kimura, “Vascular endothelium expresses 3-mercaptopuruvate sulfurrtransferase and produces hydrogen sulfide,” *Journal of Biochemistry*, vol. 146, no. 5, pp. 623–626, 2009.

[29] N. Shibuya, S. Koike, M. Tanaka et al., “A novel pathway for the production of hydrogen sulfide from D-cysteine in mammalian cells,” *Nature Communications*, vol. 4, article 1366, 2013.

[30] H. Kimura, “Production and physiological effects of hydrogen sulfide,” *Antioxidants and Redox Signaling*, vol. 20, no. 5, pp. 783–793, 2014.

[31] G. A. Benavides, G. L. Squadrito, R. W. Mills et al., “Hydrogen sulfide mediates the vasoactivity of garlic,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 46, pp. 17977–17982, 2007.

[32] B. L. Predmore, K. Kondo, S. Bhushan et al., “The polysulfide diallyl trisulfide protects the ischemic myocardium by preservation of endogenous hydrogen sulfide and increasing nitric oxide bioavailability,” *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 302, no. 11, pp. H2410–H2418, 2012.

[33] P. M. Snijder, A. S. Frenay, R. A. de Boer et al., “Exogenous administration of thiosulfate, a donor of hydrogen sulfide, attenuates Angiotensin II-induced hypertensive heart disease in rats,” *British Journal of Pharmacology*, 2014.

[34] T. Imai, Y. Kosuge, K. Endo-Umeda et al., “Protective effect of S-allyl-1-cysteine against endoplasmic reticulum stress-induced neuronal death is mediated by inhibition of calpain,” *Amino Acids*, vol. 46, no. 2, pp. 385–393, 2014.

[35] Y. Zhao, T. D. Biggs, and M. Xian, “Hydrogen sulfide (H₂S) releasing agents: chemistry and biological applications,” *Chemical Communications (Cambridge)*, vol. 50, no. 80, pp. 11788–11805, 2014.

[36] P. M. Snijder, R. A. de Boer, E. M. Bos et al., “Gaseous hydrogen sulfide protects against myocardial ischemia-reperfusion injury in mice partially independent from hypometabolism,” *PLoS ONE*, vol. 8, no. 5, article ID e63291, 2013.

[37] O. Kabil and R. Banerjee, “Redox biochemistry of hydrogen sulfide,” *The Journal of Biological Chemistry*, vol. 285, no. 29, pp. 21903–21907, 2010.

[38] T. M. Hildebrandt and M. K. Grieshaber, “Three enzymatic activities catalyze the oxidation of sulfide to sulfionate in mammalian and invertebrate mitochondria,” *FEBS Journal*, vol. 275, no. 13, pp. 3352–3361, 2008.

[39] G.-J. Lee, S. K. Kim, S. W. Kang et al., “Real-time measurement of myocardial oxygen dynamics during cardiac ischemia-reperfusion of rats,” *Analyst*, vol. 137, no. 22, pp. 5312–5319, 2012.

[40] J. Fauconnier, A. C. Meli, J. Thireau et al., “Ryanodine receptor leak mediated by caspase-8 activation leads to left ventricular injury after myocardial ischemia-reperfusion,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 32, pp. 13258–13263, 2011.

[41] C. Nastos, K. Kalimeris, N. Papoutsidakis et al., “Global consequences of liver ischemia/reperfusion injury,” *Oxidative Medicine and Cellular Longevity*, vol. 2014, Article ID 906965, 13 pages, 2014.

[42] Y. Zhai, H. Petrowsky, J. C. Hong, R. W. Busuttil, and J. W. Kupiec-Weglinski, “Ischaemia-reperfusion injury in liver transplantation—from bench to bedside,” *Nature Reviews Gastroenterology & Hepatology*, vol. 10, no. 2, pp. 79–89, 2013.

[43] E. Cure, M. Cumhur Cure, L. Tumkaya et al., “Adalimumab ameliorates abdominal aorta cross clamping which induced liver injury in rats,” *BioMed Research International*, vol. 2014, Article ID 907915, 8 pages, 2014.

[44] M. Elías-Miró, M. B. Jiménez-Castro, J. Rodés, and C. Peralta, “Current knowledge on oxidative stress in hepatic ischemia/reperfusion,” *Free Radical Research*, vol. 47, no. 8, pp. 555–568, 2013.

[45] P. Mukhopadhyay, B. Horváth, Z. Zseggler et al., “Mitochondrial reactive oxygen species generation triggers inflammatory response and tissue injury associated with hepatic ischemia-reperfusion: therapeutic potential of mitochondrially targeted antioxidants,” *Free Radical Biology and Medicine*, vol. 53, no. 5, pp. 1123–1138, 2012.

[46] K. Kang, M. Zhao, H. Jiang, G. Tan, S. Pan, and X. Sun, “Role of hydrogen sulfide in hepatic ischemia-reperfusion-induced injury in rats,” *Liver Transplantation*, vol. 15, no. 10, pp. 1306–1314, 2009.

[47] G. M. Chertow, E. Burdick, M. Honour, J. V. Bonventre, and D. W. Bates, “Acute kidney injury, mortality, length of stay, and costs in hospitalized patients,” *Journal of the American Society of Nephrology*, vol. 16, no. 11, pp. 3365–3370, 2005.

[48] Y. Wang, J. Jia, G. Aoe et al., “Hydrogen sulfide treatment protects against reperfusion injury following cerebral ischemia-reperfusion,” *Brain Research*, vol. 1496, no. 1, pp. 160–169, 2012.

[49] D. Wang, L. Shi, and L. Cai, “Mitochondrial dysfunction and oxidative stress in reperfusion injury following cerebral ischemia,” *Neurochem Research*, vol. 37, no. 5, pp. 619–627, 2012.

[50] J. Han, G. W. He, and Z. W. Chen, “Protective effect and mechanism of total flavones from *Rhododendron simsii* planch on endothelium-dependent dilatation and hyperpolarization in cerebral ischemia-reperfusion and correlation to hydrogen sulfide release in rats,” *Evidence-Based Complementary and Alternative Medicine*, vol. 2014, Article ID 904019, 11 pages, 2014.

[51] X.-M. Chen, H.-S. Chen, M.-J. Xu, and J.-G. Shen, “Targeting reactive nitrogen species: a promising therapeutic strategy for cerebral ischemia-reperfusion injury,” *Acta Pharmacologica Sinica*, vol. 34, no. 1, pp. 67–77, 2013.

[52] J. Pan, A.-A. Konstanja, B. Bateman, G. A. Ortolano, and J. Pile-Spellman, “Reperfusion injury following cerebral ischemia: pathophysiology, MR imaging, and potential therapies,” *Neuroradiology*, vol. 49, no. 2, pp. 93–102, 2007.

[53] K. Liu, Y. Sun, Z. Gu, N. Shi, T. Zhang, and X. Sun, “Mitophagy in ischaemia/reperfusion induced cerebral injury,” *Neurochemical Research*, vol. 38, no. 7, pp. 1295–1300, 2013.

[54] Y. Wang, J. Jia, G. Ao et al., “Hydrogen sulfide protects blood-brain barrier integrity following cerebral ischemia,” *Journal of Neurochemistry*, vol. 129, no. 5, pp. 827–838, 2014.

[55] H. Jang, M. Y. Oh, Y. J. Kim et al., “Hydrogen sulfide treatment induces angiogenesis after cerebral ischemia,” *Journal of Neuroscience Research*, vol. 92, no. 11, pp. 1520–1528, 2014.
[57] S. Gheibi, N. Aboutaleb, M. Khaksari et al., “Hydrogen sulfide protects the brain against ischemic reperfusion injury in a transient model of focal cerebral ischemia,” *Journal of Molecular Neuroscience*, vol. 54, no. 2, pp. 264–270, 2014.

[58] X. Lin, S. Yu, Y. Chen, J. Wu, J. Zhao, and Y. Zhao, “Neuroprotective effects of diallyl sulfide against transient focal cerebral ischemia via anti-apoptosis in rats,” *Neurological Research*, vol. 34, no. 1, pp. 32–37, 2012.

[59] C. Ren, A. Du, D. Li, J. Sui, W. G. Mayhan, and H. Zhao, “Dynamic change of hydrogen sulfide during global cerebral ischemia-reperfusion and its effect in rats,” *Brain Research*, vol. 1345, pp. 197–205, 2010.

[60] A. Bhattacharyya, R. Chattopadhyay, S. Mitra, and S. E. Crowe, “Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases,” *Physiological Reviews*, vol. 94, no. 2, pp. 329–354, 2014.

[62] H. Liu, X.-B. Bai, S. Shi, and Y.-X. Cao, “Hydrogen sulfide protects from intestinal ischaemia-reperfusion injury in rats,” *Journal of Pharmacy and Pharmacology*, vol. 61, no. 2, pp. 207–212, 2009.

[64] M. C. L. Wu, F. H. Brennan, J. P. L. Lynch et al., “The receptor for complement component C3a mediates protection from intestinal ischemia-reperfusion injuries by inhibiting neutrophil mobilization,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 110, no. 23, pp. 9439–9444, 2013.

[65] P. W. Henderson, A. L. Weinstein, A. M. Sohn, N. Jimenez, D. D. Kriigh, and J. A. Spector, “Hydrogen sulfide attenuates intestinal ischemia-reperfusion injury when delivered in the post-ischemic period,” *Journal of Gastroenterology and Hepatology*, vol. 25, no. 10, pp. 1642–1647, 2010.

[66] C. Guo, E. Liang, W. S. Masood, and X. Yan, “Hydrogen sulfide protected gastric epithelial cell from ischemia/reperfusion injury by Keap1 s-sulfhydration, MAPK dependent anti-apoptosis and NF-κB dependent anti-inflammation pathway,” *European Journal of Pharmacology*, vol. 725, no. 1, pp. 70–78, 2014.

[67] Y. Li, J.-F. Zhang, Y.-M. Zhang, and X.-B. Ma, “The protective effect of genistein postconditioning on hypoxia/reoxygenation-induced injury in human gastric epithelial cells,” *Acta Pharmacologica Sinica*, vol. 30, no. 5, pp. 576–581, 2009.

[68] J. Cui, L. Liu, J. Zou et al., “Protective effect of endogenous hydrogen sulfide against oxidative stress in gastric ischemia-reperfusion injury,” *Experimental and Therapeutic Medicine*, vol. 5, no. 3, pp. 689–694, 2013.

[69] S. A. Mard, N. Neisi, G. Solgi, M. Hassanpour, M. Darbar, and M. Maleki, “Gastroprotective effect of NaHS against mucosal lesions induced by ischemia-reperfusion injury in rat,” *Digestive Diseases and Sciences*, vol. 57, no. 6, pp. 1496–1503, 2012.

[70] C. J. Ball, A. J. Reiffel, S. Chintalapani, M. Kim, J. A. Spector, and M. R. King, “Hydrogen sulfide reduces neutrophil recruitment in hind-limb ischemia-reperfusion injury in an 1-selectin and ADAM-17-dependent manner,” *Plastic and Reconstructive Surgery*, vol. 131, no. 3, pp. 487–497, 2013.

[71] P. W. Henderson, S. P. Singh, A. L. Weinstein et al., “Therapeutic metabolic inhibition: hydrogen sulfide significantly mitigates skeletal muscle ischemia reperfusion injury in vitro and in vivo,” *Plastic and Reconstructive Surgery*, vol. 126, no. 6, pp. 1890–1898, 2010.

[72] F. Beyersdorf, “The use of controlled reperfusion strategies in cardiac surgery to minimize ischaemia/reperfusion damage,” *Cardiovascular Research*, vol. 83, no. 2, pp. 262–268, 2009.

[73] P. W. Henderson, N. Jimenez, J. Ruffino et al., “Therapeutic delivery of hydrogen sulfide for salvage of ischemic skeletal muscle after the onset of critical ischemia,” *Journal of Vascular Surgery*, vol. 53, no. 3, pp. 785–791, 2011.

[74] W. Chen, G. Zheng, S. Yang et al., “CYP2J2 and EETs protect against oxidative stress and apoptosis in vivo and in vitro following lung ischemia/reperfusion,” *Cellular Physiology and Biochemistry*, vol. 33, no. 6, pp. 1663–1680, 2014.

[75] M. de Perrot, M. Liu, T. K. Waddell, and S. Keshavjee, “Ischemia-reperfusion-induced lung injury,” *American Journal of Respiratory and Critical Care Medicine*, vol. 167, no. 4, pp. 490–511, 2003.

[76] W. A. den Hengst, J. F. Gielis, J. Y. Lin, P. E. van Schil, L. J. de Windt, and A. L. Moens, “Lung ischemia-reperfusion injury: a molecular and clinical view on a complex pathophysiological process,” *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 299, no. 5, pp. H1283–H1299, 2010.

[77] J. Zhang, J.-S. Wang, Z.-K. Zheng et al., “Participation of autophagy in lung ischemia-reperfusion injury in vivo,” *Journal of Surgical Research*, vol. 182, no. 2, pp. E79–E87, 2013.

[78] J. M. Dodd-o, M. L. Hristopoulos, L. E. Welsh-Servinsky, C. G. Tankersley, and D. B. Pearse, “Strain-specific differences in sensitivity to ischemia-reperfusion lung injury in mice,” *Journal of Applied Physiology*, vol. 100, no. 5, pp. 1590–1595, 2006.

[79] J.-H. Cho, X. Mu, S. W. Wang, and W. H. Klein, “Retinal ganglion cell death and optic nerve degeneration by genetic ablation in adult mice,” *Experimental Eye Research*, vol. 88, no. 3, pp. 542–552, 2009.

[80] B.-J. Kim, T. A. Braun, R. J. Wordinger, and A. F. Clark, “Progressive morphological changes and impaired retinal function associated with temporal regulation of gene expression after retinal ischemia/reperfusion injury in mice,” *Molecular Neurodegeneration*, vol. 8, no. 1, article 21, 2013.

[81] K. Andreeva, M. Zhang, W. Fan et al., “Time-dependent gene profiling indicates the presence of different phases for ischemia/reperfusion injury in retina,” *Ophthalmology and Eye Diseases*, vol. 6, pp. 43–54, 2014.

[82] M.-H. Sun, J.-H. S. Pang, S.-L. Chen et al., “Retinal protection from acute glaucoma-induced ischemia-reperfusion injury through pharmacologic induction of heme oxygenase-1,” *Investigative Ophthalmology & Visual Science*, vol. 51, no. 9, pp. 4798–4808, 2010.

[83] N. N. Osborne, R. J. Casson, J. P. M. Wood, G. Chidlow, M. Graham, and J. Melena, “Retinal ischemia: mechanisms of damage and potential therapeutic strategies,” *Progress in Retinal and Eye Research*, vol. 23, no. 1, pp. 91–147, 2004.

[84] J. Biermann, W. A. Lagrèze, N. Schallner, C. I. Schwer, and U. Goebel, “Inhalative preconditioning with hydrogen sulfide attenuated apoptosis after retinal ischemia/reperfusion injury,” *Molecular Vision*, vol. 17, pp. 1275–1286, 2011.

[85] N. N. Osborne, D. Ji, A. S. A. Majid, R. J. Fawcett, A. Sparatore, and P. Del Soldato, “AGS67, a hydrogen sulfide-releasing
derivative of latanoprost acid, attenuates retinal ischemia and oxidative stress to RGC-5 cells in culture,” *Investigative Ophthalmology and Visual Science*, vol. 51, no. 1, pp. 284–294, 2010.

[86] L. Li, M. Whiteman, Y. Y. Guan et al., “Characterization of a novel, water-soluble hydrogen sulfide-releasing molecule (GYY4137): new insights into the biology of hydrogen sulfide,” *Circulation*, vol. 117, no. 18, pp. 2351–2360, 2008.

[87] Z.-W. Lee, X.-Y. Teo, E. Y.-W. Tay et al., “Utilizing hydrogen sulfide as a novel anti-cancer agent by targeting cancer therapy glycophorin and pH imbalance,” *British Journal of Pharmacology*, vol. 171, no. 18, pp. 4322–4336, 2014.

[88] C. N. Wang, Y. J. Liu, G. L. Duan et al., “CBS and CSE are critical for maintenance of mitochondrial function and gluconcyclotide production in adrenal cortex,” *Antioxidants & Redox Signaling*, vol. 21, no. 16, pp. 2192–2207, 2014.

[89] N. Ning, J. Zhi, Y. Du, X. Gao, C. Liu, and J. Li, “Dysregulation of hydrogen sulphide metabolism impairs oviductal transport of embryos,” *Nature Communications*, vol. 5, p. 4107, 2014.

[90] H. Robinson and S. Wray, “A new slow releasing, H$_2$S generating compound, GYY4137 relaxes spontaneous and oxytocin-stimulated contractions of human and rat pregnant myometrium,” *PLoS ONE*, vol. 7, no. 9, Article ID e46278, 2012.

[91] E. Grambow, F. Mueller-Graf, E. Delyagina, M. Frank, A. Kuhla, and B. Vollmar, “Effect of the hydrogen sulfide donor GYY4137 on platelet activation and microvascular thrombus formation in mice,” *Platelets*, vol. 25, no. 3, pp. 166–174, 2014.

[92] J. Jia, Y. Xiao, W. Wang et al., “Differential mechanisms underlying neuroprotection of hydrogen sulfide donors against oxidative stress,” *Neurochemistry International*, vol. 62, no. 8, pp. 1072–1078, 2013.

[93] C. K¨ohn, J. Schleifenbaum, I. A. Szij´art´oe et al., “Differential effects of cystathionine-γ-lyase-dependent vasodilator H$_2$S in periadventitial vasoregulation of rat and mouse aortas,” *PLoS ONE*, vol. 7, no. 8, Article ID e41951, 2012.

[94] X. Zhou, Y. Cao, G. Ao et al., “CaMKKζ-dependent activation of AMP-activated protein kinase is critical to suppressive effects of hydrogen sulfide on neuroinflammation,” *Antioxidants & Redox Signaling*, vol. 21, no. 12, pp. 1741–1758, 2014.

[95] B. Szczesny, K. Módis, K. Yanagi et al., “AP39, a novel mitochondrial-targeted hydrogen sulfide donor, stimulates cellular bioenergetics, exerts cytoprotective effects and protects against the loss of mitochondrial DNA integrity in oxidatively stressed endothelial cells in vitro,” *Nitric Oxide: Biology and Chemistry*, vol. 41, pp. 120–130, 2014.

[96] J. C. Foster, C. R. Powell, S. C. Radzinski, and J. B. Matson, “S-aryloxythiooximes: a facile route to hydrogen sulfide releasing compounds with structure-dependent release kinetics,” *Organic Letters*, vol. 16, no. 6, pp. 1558–1561, 2014.

[97] J. Kan, W. Guo, C. Huang, G. Bao, Y. Zhu, and Y. Z. Zhu, “S-propargyl-cysteine, a novel water-soluble modulator of endogenous hydrogen sulfide, promotes angiogenesis through activation of signal transducer and activator of transcription 3,” *Antioxidants & Redox Signaling*, vol. 20, no. 15, pp. 2303–2316, 2014.

[98] K. Ma, Y. Liu, Q. Zhu et al., “H$_2$S donor, S-propargyl-cysteine, increases CSE in SGC-7901 and cancer-induced mice: evidence for a novel anti-cancer effect of endogenous H$_2$S?” *PLoS ONE*, vol. 6, no. 6, Article ID e20525, 2011.

[99] Q. Wang, X.-L. Wang, H.-R. Liu, P. Rose, and Y.-Z. Zhu, “Protective effects of cysteine analogues on acute myocardial ischemia: novel modulators of endogenous H$_2$S production,” *Antioxidants and Redox Signaling*, vol. 12, no. 10, pp. 1155–1165, 2010.

[100] L.-L. Pan, X.-H. Liu, Q.-H. Gong, and Y.-Z. Zhu, “S-propargyl-cysteine (SPRC) attenuated lipopolysaccharide-induced inflammatory response in H9c2 cells involved in a hydrogen sulfide-dependent mechanism,” *Amino Acids*, vol. 41, no. 1, pp. 205–215, 2011.

[101] K. Kondo, S. Bhushan, A. L. King et al., “H$_2$S protects against pressure overload-induced heart failure via upregulation of endothelial nitric oxide synthase,” *Circulation*, vol. 127, no. 10, pp. 1116–1127, 2013.

[102] F. Liu, D.-D. Chen, X. Sun et al., “Hydrogen sulfide improves wound healing via restoration of endothelial progenitor cell functions and activation of angiopoietin-1 in type 2 diabetes,” *Diabetes*, vol. 63, no. 5, pp. 1763–1778, 2014.

[103] A. Martelli, L. Testai, V. Citi et al., “Arylthioamides as H$_2$S donors: l-cysteine-activated releasing properties and vascular effects in vitro and in vivo,” *ACS Medicinal Chemistry Letters*, vol. 4, no. 10, pp. 904–908, 2013.

[104] Y. Zhao, H. Wang, and M. Xian, “Cysteine-activated hydrogen sulfide (H$_2$S) donors,” *Journal of the American Chemical Society*, vol. 133, no. 1, pp. 15–17, 2011.

[105] D. Giustarini, A. Milzani, I. Dalle-Donne, D. Tsikas, and R. Rossi, “N-acetylcysteine ethyl ester (NACET): a novel lipophilic cell-permeable cysteine derivative with an unusual pharmacokinetic feature and remarkable antioxidant potential,” *Biochemical Pharmacology*, vol. 84, no. 11, pp. 1522–1533, 2012.

[106] A. Martelli, L. Testai, V. Citi et al., “Pharmacological characterization of the vascular effects of aryl isothiocyanates: is hydrogen sulfide the real player?” *Vascular Pharmacology*, vol. 60, no. 1, pp. 32–41, 2014.

[107] E. Ekundi-Valentim, K. T. Santos, E. A. Camargo et al., “Differing effects of exogenous and endogenous hydrogen sulhide in carrageenan-induced knee joint synovitis in the rat: research paper,” *British Journal of Pharmacology*, vol. 159, no. 7, pp. 1463–1474, 2010.

[108] J. V. R. Medeiros, V. H. Bezerra, A. S. Gomes et al., “Hydrogen sulfide prevents ethanol-induced gastric damage in mice: role of ATP-sensitive potassium channels and capsaicin-sensitive primary afferent neurons,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 330, no. 3, pp. 764–770, 2009.

[109] Z. Zhou, M. Von Wantoch Rekowski, C. Coletta et al., “Thioglycine and l-thioline: biologically active H$_2$S donors,” *Bioorganic and Medicinal Chemistry*, vol. 20, no. 8, pp. 2675–2678, 2012.

[110] Y. Zhao, S. Bhushan, C. Yang et al., “Controllable hydrogen sulfide donors and their activity against myocardial ischemia-reperfusion injury,” *ACS Chemical Biology*, vol. 8, no. 6, pp. 1283–1290, 2013.

[111] N. Fukushima, N. Ieda, K. Sasakura et al., “Synthesis of a photocontrollable hydrogen sulfide donor using ketoprofenate photocages,” *Chemical Communications*, vol. 50, no. 5, pp. 587–589, 2014.

[112] V. Citi, A. Martelli, L. Testai, A. Marino, M. Breschi, and V. Rossi, “Hydrogen sulfide releasing capacity of natural isothiocyanates: is it a reliable explanation for the multiple biological effects of Brassicaceae?” *Planta Medica*, vol. 80, no. 8-9, pp. 610–613, 2014.

[113] U. Hasegawa and A. J. van der Vlies, “Design and synthesis of polymeric hydrogen sulfide donors,” *Bioconjugate Chemistry*, vol. 25, no. 7, pp. 1290–1300, 2014.
S. Musaффar, J. Y. Jeremy, A. Sparatore, P. Del Soldato, G. D. Rossoni, B. Manfredi, V. Tazzari et al., "Activity of a new dithiolethione-modified nonsteroidal anti-inflammatory drugs in human estrogen receptor-negative breast cancer," *Cancer Research*, vol. 72, no. 9, pp. 2394–2404, 2012.

J. S. Isenberg, Y. Jia, L. Field et al., "Modulation of angiogenesis by dithiolethione-modified NSAIDs and valproic acid," *British Journal of Pharmacology*, vol. 151, no. 1, pp. 63–72, 2007.

M. Lee, V. Tazzari, D. Giustarini et al., "Effects of hydrogen sulfide-releasing L-DOPA derivatives on glial activation: potential for treating Parkinson disease," *Journal of Biological Chemistry*, vol. 285, no. 23, pp. 17318–17328, 2010.

X.-Q. Tang, R.-Q. Chen, L. Dong et al., "Role of paraoxonase-1 in the protection of hydrogen sulfide-donating sildenafil (ACS6) against homocysteine-induced neurotoxicity," *Journal of Molecular Neuroscience*, vol. 50, no. 1, pp. 70–77, 2013.

S. Muzaffar, J. Y. Jeremy, A. Sparatore, P. Del Soldato, G. D. Angelini, and N. Shukla, "H₂S-donating sildenafil (ACS6) inhibits superoxide formation and gp91 phox expression in arterial endothelial cells: Role of protein kinases A and G," *British Journal of Pharmacology*, vol. 155, no. 7, pp. 984–994, 2008.

Q. Huang, A. Sparatore, P. Del Soldato, L. Wu, K. Desai, and R. Nagaraj, "Hydrogen sulfide releasing aspirin, ACSI4, attenuates high glucose-induced increased methylglyoxal and oxidative stress in cultured vascular smooth muscle cells," *PLoS ONE*, vol. 9, no. 6, Article ID e97315, 2014.

H. Zhang, C. Guo, A. Zhang et al., "Effect of S-aspirin, a novel hydrogen-sulfide-releasing aspirin (ACSI4), on atherosclerosis in apoE-deficient mice," *European Journal of Pharmacology*, vol. 697, no. 1–3, pp. 106–116, 2012.

J. Pircher, F. Fochler, T. Czermak et al., "Hydrogen sulfide-releasing aspirin derivative acs14 exerts strong antithrombotic effects in vitro and in vivo," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 32, no. 12, pp. 2884–2891, 2012.

G. Rossoni, B. Manfredi, V. Tazzari et al., "Activity of a new hydrogen sulfide-releasing aspirin (ACSI4) on pathological cardiovascular alterations induced by glutathione depletion in rats," *European Journal of Pharmacology*, vol. 648, no. 1–3, pp. 139–145, 2010.

D. Giustarini, P. Del Soldato, A. Sparatore, and R. Rossi, "Modulation of thiol homeostasis induced by H₂S-releasing aspirin," *Free Radical Biology and Medicine*, vol. 48, no. 9, pp. 1263–1272, 2010.

S. E. Bass, P. Sienkiewicz, C. J. MacDonald et al., "Novel dithiolethione-modified nonsteroidal anti-inflammatory drugs in human hepatoma HepG2 and colon LS180 cells," *Clinical Cancer Research*, vol. 15, no. 6, pp. 1964–1972, 2009.

J. Frantzias, J. G. Logan, P. Mollat et al., "Hydrogen sulphide-releasing diclofenac derivatives inhibit breast cancer-induced osteolastogenesis in vitro and prevent osteolysis ex vivo," *British Journal of Pharmacology*, vol. 165, no. 6, pp. 1914–1925, 2012.
M. Chattopadhyay, R. Kodela, K. R. Olson, and K. Kashfi, “NOSH-aspirin (NBS-1120), a novel nitric oxide- and hydrogen sulfide-releasing hybrid is a potent inhibitor of colon cancer cell growth in vitro and in a xenograft mouse model,” *Biochemical and Biophysical Research Communications*, vol. 419, no. 3, pp. 523–528, 2012.

M. Lee, E. Mcgeer, R. Kodela, K. Kashfi, and P. L. Mcgeer, “NOSH-aspirin (NBS-1120), a novel nitric oxide and hydrogen sulfide releasing hybrid, attenuates neuroinflammation induced by microglial and astrocytic activation: a new candidate for treatment of neurodegenerative disorders,” *Glia*, vol. 61, no. 10, pp. 1724–1734, 2013.

R. Kodela, M. Chattopadhyay, and K. Kashfi, “Synthesis and biological activity of NOSH-naproxen (AVT-219) and NOSH-sulindac (AVT-18A) as potent anti-inflammatory agents with chemotherapeutic potential,” *MedChemComm*, vol. 4, no. 11, pp. 1472–1481, 2013.

G. Rossoni, A. Sparatore, V. Tazzari, B. Manfredi, P. D. Soldato, and F. Berti, “The hydrogen sulphide-releasing derivative of diclofenac protects against ischemia-reperfusion injury in the isolated rabbit heart,” *British Journal of Pharmacology*, vol. 153, no. 1, pp. 100–109, 2008.

M. Bucci, V. Vellecco, A. Cantalupo et al., “Hydrogen sulfide accounts for the peripheral vascular effects of zofenopril independently of ACE inhibition,” *Cardiovascular Research*, vol. 102, no. 1, pp. 138–147, 2014.

K. Issa, A. Kimmoun, S. Collin et al., “Compared effects of inhibition and exogenous administration of hydrogen sulphide in ischaemia-reperfusion injury,” *Critical Care*, vol. 17, article R129, 2013.

A. Sivarajah, M. Collino, M. Yasin et al., “Anti-apoptotic and anti-inflammatory effects of hydrogen sulfide in a rat model of regional myocardial I/R,” *Shock*, vol. 31, no. 3, pp. 267–274, 2009.

M. G. Alves, A. F. Soares, R. A. Carvalho, and P. J. Oliveira, “Sodium hydrosulfide improves the protective potential of the cardioplegic histidine buffer solution,” *European Journal of Pharmacology*, vol. 654, no. 1, pp. 60–67, 2011.

Y. Ji, Q.-F. Pang, G. Xu, L. Wang, J.-K. Wang, and Y.-M. Zeng, “Exogenous hydrogen sulfide postconditioning protects isolated rat hearts against ischemia-reperfusion injury,” *European Journal of Pharmacology*, vol. 587, no. 1–3, pp. 1–7, 2008.

Y.-H. Sun, F. Liu, Y. Chen, and Y.-C. Zhu, “Hydrogen sulfide decreases the levels of ROS by inhibiting mitochondrial complex IV and increasing SOD activities in cardiomyocytes under ischemia/reperfusion,” *Biochemical and Biophysical Research Communications*, vol. 421, no. 2, pp. 164–169, 2012.

H.-F. Luan, Z.-B. Zhao, Q.-H. Zhao, P. Zhu, M.-Y. Xiu, and Y. Ji, “Hydrogen sulfide postconditioning protects isolated rat hearts against ischemia and reperfusion injury mediated by the JAK2/STAT3 survival pathway,” *Brazilian Journal of Medical and Biological Research*, vol. 45, no. 10, pp. 898–905, 2012.

M. Bliksoen, M.-L. Kaljusto, J. Vaage, and K.-O. Stensløkken, “Effects of hydrogen sulfide on ischaemia-reperfusion injury and ischaemic preconditioning in the isolated, perfused rat heart,” *European Journal of Cardio-thoracic Surgery*, vol. 34, no. 2, pp. 344–349, 2008.

D. J. Elsey, R. C. Fowkes, and G. F. Baxter, “L-cysteine stimulates hydrogen sulfide synthesis in myocardium associated with attenuation of ischemia-reperfusion injury,” *Journal of Cardiovascular Pharmacology and Therapeutics*, vol. 15, no. 1, pp. 53–59, 2010.

Y. Gao, X. Yao, Y. Zhang et al., “The protective role of hydrogen sulfide in myocardial ischemia-reperfusion-induced injury in diabetic rats,” *International Journal of Cardiology*, vol. 152, no. 2, pp. 177–183, 2011.

J. S. Bian, C. Y. Qian, T. T. Pan et al., “Role of hydrogen sulfide in the cardioprotection caused by ischemic preconditioning in the rat heart and cardiac myocytes,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 316, no. 2, pp. 670–678, 2006.

Y. Hu, X. Chen, T.-T. Pan et al., “Cardioprotection induced by hydrogen sulfide preconditioning involves activation of ERK and PI3K/Akt pathways,” *Pflugers Archiv European Journal of Physiology*, vol. 455, no. 4, pp. 607–616, 2008.

L.-F. Hu, T.-T. Pan, K. L. Neo, Q. C. Yong, and J.-S. Bian, “Cyclooxygenase-2 mediates the delayed cardioprotection induced by hydrogen sulfide preconditioning in isolated rat cardiomyocytes,” *Pflugers Archiv European Journal of Physiology*, vol. 455, no. 6, pp. 971–978, 2008.

N. R. Soda, R. T. Clements, J. Feng et al., “Hydrogen sulfide therapy attenuates the inflammatory response in a porcine model of myocardial ischemia/reperfusion injury,” *Journal of Thoracic and Cardiovascular Surgery*, vol. 138, no. 4, pp. 977–984, 2009.

N. R. Soda, R. T. Clements, J. Feng et al., “The effects of therapeutic sulfide on myocardial apoptosis in response to ischemia-reperfusion injury,” *European Journal of Cardio-Thoracic Surgery*, vol. 33, no. 5, pp. 906–913, 2008.

D. Johansen, K. Ytrehus, and G. F. Baxter, “Exogenous hydrogen sulfide (H2S) protects against regional myocardial ischemia-reperfusion injury. Evidence for a role of KATP channels,” *Basic Research in Cardiology*, vol. 101, no. 1, pp. 53–60, 2006.

F. Ganster, M. Burban, M. de la Bourdonnaye et al., “Effects of hydrogen sulfide on hemodynamics, inflammatory response and oxidative stress during resuscitated hemorrhagic shock in rats,” *Critical Care*, vol. 14, no. 5, article R165, 2010.

L. L. Yao, X. W. Huang, Y. G. Wang, Y. X. Cao, C. C. Zhang, and Y. C. Zhu, “Hydrogen sulfide protects cardiomyocytes from hypoxia/reoxygenation-induced apoptosis by preventing GSK-3β-dependent opening of mPTP,” *The American Journal of Physiology—Heart and Circulatory Physiology*, vol. 298, no. 5, pp. H1310–H1319, 2010.

B. F. Peake, C. K. Nicholson, J. P. Lambert et al., “Hydrogen sulfide preconditionings the db/db diabetic mouse heart against ischemia-reperfusion injury by activating Nrf2 signaling in an Erk-dependent manner,” *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 304, no. 9, pp. H1215–H1224, 2013.

X. Yao, G. Tan, C. He et al., “Hydrogen sulfide protects cardiomyocytes from myocardial ischemia-reperfusion injury by enhancing phosphorylation of apoptosis repressor with caspase recruitment domain,” *The Tohoku Journal of Experimental Medicine*, vol. 226, no. 4, pp. 275–285, 2012.

J. W. Elrod, J. W. Calvert, J. Morrison et al., “Hydrogen sulfide attenuates myocardial ischemia-reperfusion injury by preservation of mitochondrial function,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 39, pp. 15560–15565, 2007.

S. Toldo, A. Das, E. Mezzaroma et al., “Induction of microRNA-21 with exogenous hydrogen sulfide attenuates myocardial ischemic and inflammatory injury in mice,” *Circulation: Cardiovascular Genetics*, vol. 7, no. 3, pp. 311–320, 2014.
J. W. Calvert, S. Jha, S. Gundewar et al., “Hydrogen sulfide mediates cardioprotection through nrf2 signaling,” Circulation Research, vol. 105, no. 4, pp. 365–374, 2009.

W.-J. Zhang, Z.-X. Shi, B.-B. Wang, Y.-J. Cui, J.-Z. Guo, and B. Li, “Allitrudium mimics effect of ischemic preconditioning by activation of protein kinase C,” Acta Pharmacologica Sinica, vol. 22, no. 2, pp. 132–136, 2001.

Y. Zhou, D. Wang, X. Gao, K. Lew, A. M. Richards, and P. Wang, “mTORC2 phosphorylation of Akt: a possible mechanism for hydrogen sulfide-induced cardioprotection,” PLoS ONE, vol. 9, no. 6, Article ID e99665, 2014.

A. Sivarajah, M. C. McDonald, and C. Thiemermann, “The production of hydrogen sulfide limits myocardial ischemia and reperfusion injury and contributes to the cardioprotective effects of preconditioning with endotoxin, but not ischemia in the rat,” Shock, vol. 26, no. 2, pp. 154–161, 2006.

B. Kang, J. Hong, J. Xiao et al., “Involvement of miR-1 in the protective effect of hydrogen sulfide against cardiomyocyte apoptosis induced by ischemia/reperfusion,” Molecular Biology Reports, vol. 41, no. 10, pp. 6845–6853, 2014.

S. Minamishima, M. Bougaki, P. Y. Sips et al., “Hydrogen sulfide improves survival after cardiac arrest and cardiopulmonary resuscitation via a nitric oxide synthase 3-dependent mechanism in mice,” Circulation, vol. 120, no. 10, pp. 888–896, 2009.

Y. Zhuo, P.-F. Chen, A.-Z. Zhang, H. Zhong, C.-Q. Chen, and Y.-Z. Zhu, “Cardioprotective effect of hydrogen sulfide in ischemic reperfusion experimental rats and its influence on expression of survivin gene,” Biological and Pharmaceutical Bulletin, vol. 32, no. 8, pp. 1406–1410, 2009.

R. M. Osipov, M. P. Robich, J. Feng et al., “Effect of hydrogen sulfide in a porcine model of myocardial ischemia-reperfusion: comparison of different administration regimens and characterization of the cellular mechanisms of protection,” Journal of Cardiovascular Pharmacology, vol. 54, no. 4, pp. 287–297, 2009.

Y. Chen, Z. Liu, and X. Xie, “Hydrogen sulphide attenuates renal and cardiac injury after total hepatic ischemia and reperfusion,” Journal of Surgical Research, vol. 164, no. 2, pp. e305–e313, 2010.

I. H. Shaik, J. M. George, T. J. Thekkumkara, and R. Mehvar, “Protective effects of diallyl sulfide, a garlic constituent, on the warm hepatic ischemia-reperfusion injury in a rat model,” Pharmacological Research, vol. 25, no. 10, pp. 2231–2242, 2008.

S. Jha, J. W. Calvert, M. R. Duranski, A. Ramachandran, and D. J. Lefer, “Hydrogen sulfide attenuates hepatic ischemia-reperfusion injury: role of antioxidant and antiapoptotic signaling,” American Journal of Physiology—Heart and Circulatory Physiology, vol. 295, no. 2, pp. H801–H806, 2008.

E. M. Bos, P. M. Snijder, H. Jekel et al., “Beneficial effects of gaseous hydrogen sulfide in hepatic ischemia/reperfusion injury,” Transplant International, vol. 25, no. 8, pp. 897–908, 2012.

P. Cheng, F. Wang, K. Chen et al., “Hydrogen sulfide ameliorates ischemia/reperfusion-induced hepatitis by inhibiting apoptosis and autophagy pathways,” Mediators of Inflammation, vol. 2014, Article ID 935251, 16 pages, 2014.

Q. Zhang, H. Fu, H. Zhang et al., “Hydrogen sulfide preconditioning protects rat liver against ischemia/reperfusion injury by activating Akt-GSK-3β signaling and inhibiting mitochondrial permeability transition,” PLoS ONE, vol. 8, no. 9, Article ID e74422, 2013.

E. M. Bos, H. G. D. Leuvenink, P. M. Snijder et al., “Hydrogen sulfide-induced hypometabolism prevents renal ischemia/reperfusion injury,” Journal of the American Society of Nephrology, vol. 20, no. 9, pp. 1901–1905, 2009.