Implications of Hydrogen Sulfide in Development of Pulmonary Hypertension

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Abstract: The pathological mechanisms underlying pulmonary hypertension (PH), as well as its treatment strategy, are crucial issues in this field. This review aimed to summarize the pathological mechanisms by which the hydrogen sulfide (H₂S) pathway contributes to PH development and its future implications. The data in this review were obtained from Medline and PubMed sources up to 2022 using the search terms “hydrogen sulfide” and “pulmonary hypertension”. In the review, we discussed the significance of endogenous H₂S pathway alteration in PH development and showed the advance of the role of H₂S as the third gasotransmitter in the mechanisms for hypoxic PH, monocrotaline-induced PH, high blood flow-induced PH, and congenital heart disease-associated PH. Notably, H₂S plays a crucial role in the development of PH via certain mechanisms, such as inhibiting the proliferation of pulmonary artery smooth muscle cells, suppressing the inflammation and oxidative stress of pulmonary artery endothelial cells, inducing pulmonary artery smooth muscle cell apoptosis, and interacting with other gaseous signaling pathways. Recently, a variety of H₂S donors were developed, including naturally occurring donors and synthetic H₂S donors. Therefore, understanding the role of H₂S in PH development may help in further exploring novel potential therapeutic targets of PH.

Keywords: hydrogen sulfide; pulmonary hypertension; remodeling; pulmonary artery

1. Introduction

Pulmonary hypertension (PH) is regarded as a fatal pathophysiological process, with abnormally elevated pulmonary artery pressure (PAP) and even right ventricular dysfunction failure in some cases [1]. A mean PAP of up to 20 mmHg at sea level and a determination of right heart catheterization at rest are the criteria used to diagnose PH [2]. PH affects approximately 1% of the global population, i.e., a prevalence of approximately 25 cases per 1 million people [2–5]. Additionally, it usually has a poor prognosis, with high disability and mortality rates. Once diagnosed, it is sometimes difficult to cure and can be life-threatening in severe cases [6,7]. Therefore, it is extremely important to explore the mechanisms of PH development.

The endogenous gasotransmitters, including nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H₂S), and sulfur dioxide (SO₂) [8–18], with unique properties, such as rapid generation, fast transmission, extensive functions, and short half-lives, play vital roles in the pathogenesis of PH [19–21]. Great progress has been made in understanding the involvement of these gasotransmitters in the pathogenesis of PH [17,18,21].

Endogenous H₂S, a third gasotransmitter, is involved in the development of a variety of cardiovascular diseases [17,18,22–24]. H₂S is mainly catalyzed by enzymatic pathways, and it is also regulated by several metabolic pathways. It exerts important cardiovascular physiological effects [8,10,13]. For instance, it controls the vascular tone, reduces blood
pressure and PAP, inhibits the vascular smooth muscle cell (VSMC) proliferation, regulates the endothelial inflammatory response, induces VSMC apoptosis, and inhibits vascular collagen remodeling [17,18] (Figure 1).

Figure 1. The cardiovascular physiological effect of H$_2$S. H$_2$S: hydrogen sulfide; VSMCs: vascular smooth muscle cells.

The downregulated endogenous H$_2$S pathway has been observed in cardiovascular and pulmonary vascular diseases, such as PH, hypertension, atherosclerosis, ischemic myocardium, cardiac injury, heart failure, and septic shock [10,13,17,18,21]. However, exogenous supplementation with H$_2$S or H$_2$S donors can halt the progression of these cardiovascular diseases.

In the present review article, we discussed the biological origin of the endogenous H$_2$S in cardiovascular cells, and the role of endogenous H$_2$S in the development of PH, as well as the mechanisms. In addition, we discussed the crucial role of H$_2$S in the different types of PH, including hypoxic PH (HPH), monocrotaline (MCT)-induced PH, high blood flow-induced PH, congenital heart disease (CHD)-associated PH, and chronic obstructive pulmonary disease (COPD)-associated PH.

2. Biological Origin of H$_2$S in the Cell

H$_2$S is regarded as an important gasotransmitter in the regulation of various biological and pathophysiological processes [17,18,25]. H$_2$S shows an increased solubility in lipids and aqueous solution, with an efficient capability of crossing plasma membranes. The generation pathways of endogenous H$_2$S in the cell include the enzymatic pathway and non-enzymatic pathway. It is preliminarily produced by the enzyme-catalyzed reaction in the cytoplasm, using L-cysteine (L-Cys) as a substrate. The key enzymes mainly consist of cystathionine-γ-lyase (CSE), cystathionine-β-synthase (CBS), 3-mercaptopyruvate sulfur transferase (3-MST), and cysteine aminotransferase (CAT) [17,25]. In the cytoplasm, H$_2$S is catalyzed by CSE and CBS with substrates L-cysteine and L-homocysteine (Hcy). 3-MST, in combination with CAT to generate H$_2$S from L-cysteine, is demonstrated in both cytoplasm and mitochondria. It is also reported that 3-MST can generate H$_2$S with substrate D-cysteine, in the coordination of D-amino acid oxidase. The expressions of these key enzymes are tissue-specific. CSE is abundant in the thoracic aorta, liver, portal vein, ileum, and non-vasculature. CBS is mainly expressed in the brain, kidney, and liver. 3-MST plays a role in regulating H$_2$S in the aorta, kidney, brain, and liver. CSE exerts a key effect on...
H₂S generation in the cardiovascular system. However, it is different from the related enzymatic generation pathways, and the non-enzymatic reaction of H₂S production is partially catalyzed by the synergistic action of VitB6 and iron with cysteine as a substrate, in the heart, lung, spleen, muscles, plasma, and bone marrow, as well as especially in erythrocytes [17,25].

3. Role of H₂S in HPH

The pathophysiological processes of HPH mainly include progressive pulmonary vasoconstriction, pulmonary vascular inflammation, pulmonary vascular oxidative stress, and pulmonary vascular structural remodeling [1,5,6]. In early 2003 [26], our team, for the first time, showed the significance of H₂S in pulmonary circulation and reported that H₂S levels in lung tissues and plasma were reduced. Moreover, the expression and activity of CSE were inhibited in the pulmonary artery tissues and lung tissues of HPH rats. Interestingly, after the supplementation with an H₂S donor, PAP was significantly reduced, and the pulmonary vascular structural remodeling was alleviated [26]. Studies also elucidated that endogenous H₂S inhibits the formation of HPH, and the downregulation of the endogenous H₂S pathway is a key mechanism for the progression of HPH [27–30]. Therefore, the insufficient H₂S production promotes HPH.

H₂S controls HPH by employing the following mechanisms [26–33] (Figure 2): (1) relaxing vascular smooth muscles by mainly opening the K<sub>ATP</sub> channel on VSMCs; (2) directly repressing the hypoxic pulmonary artery SMC (PASMC) proliferation and inhibiting hypoxia-induced cell proliferation through the upregulation of cyclooxygenase-2/prostaglandin; (3) promoting hypoxia-induced apoptosis of PASMCs; (4) effectively inhibiting endoplasmic reticulum stress via suppressing the reduced nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX-4) expression and activity [30]; and (5) inhibiting the pulmonary extracellular matrix (ECM) accumulation. Of note, collagen and elastin gradually accumulate in an atypical manner in the adventitia of pulmonary arterioles in HPH [28]. In a hypoxic rat model, exogenous H₂S donors can reduce the production of pulmonary artery collagen, elastin, and transforming growth factor-β3 and inhibit the expression of procollagen mRNA. These results suggest that endogenous H₂S can inhibit collagen and elastin synthesis, promote collagen degradation, and alleviate hypoxic pulmonary vascular remodeling [28].

**Figure 2.** The role of H₂S in hypoxic pulmonary artery hypertension. H₂S: hydrogen sulfide; PASMCs: pulmonary arterial smooth muscle cells; COX-2: cyclooxygenase-2; PGI₂: prostaglandin; ERS: endoplasmic reticulum stress; NOX4: nicotinamide adenine dinucleotide phosphate oxidase 4; ECM: extracellular matrix.
Clinically, HPH is an important pathological change in patients with COPD partially due to airway obstruction-induced hypoxia. Yuan et al. found that serum H\textsubscript{2}S concentration in patients suffering from the acute exacerbation of COPD (AECOPD) with PH was lower than that in patients suffering from AECOPD without PH and healthy population [34]. Furthermore, the serum H\textsubscript{2}S in the AECOPD patients was negatively correlated with pulmonary artery systolic pressure (PASP). Similarly, the expression of CSE in the pulmonary artery of patients suffering from stable COPD with PH was lower than that in patients suffering from stable COPD without PH and healthy controls. Mechanistically, the upregulated NOX4/reactive oxygen species (NOX4/ROS) pathway might be involved in the possible mechanisms by which the deficiency of endogenous H\textsubscript{2}S contributes to the development of COPD-associated PH [34].

4. Role of H\textsubscript{2}S in MCT-Induced PH

PH is a progressive disease due to increased PAP and right ventricular failure [35]. MCT-induced PH is used as a classical animal model of PH in the experiment [36–38]. MCT, a toxic alkaloid, can lead to the proliferation of PASMC and inflammation of endothelial cells, even causing right heart dysfunction resulting from right cardiac overloading [36]. Feng et al. [37] showed that the endogenous H\textsubscript{2}S/CSE was downregulated in rats suffering from MCT-induced PH, and the supplement of H\textsubscript{2}S donor reduced PAP and relieved vascular structural remodeling, thus significantly improving the progression of PH. Moreover, this study demonstrated that the downregulated endogenous H\textsubscript{2}S/CSE pathway was related to pulmonary vascular inflammation in pulmonary hypertensive rats. Therefore, H\textsubscript{2}S exhibited a protective effect on MCT-induced PH.

Other studies revealed the underlying mechanisms by which H\textsubscript{2}S was involved in the MCT-induced PH [37–41]. H\textsubscript{2}S inhibited the inflammation of pulmonary arterial endothelial cells and prevented pulmonary vascular remodeling in MCT-induced PH, probably through inhibiting the nuclear factor kappa B (NF-\kappa B) signaling pathway and endothelial–mesenchymal transition in pulmonary arteries [37]. Furthermore, in vivo and in vitro findings demonstrated that endogenous H\textsubscript{2}S directly deactivated the inhibitor of the \kappa B kinase subunit \beta (IKK\beta) by sulfhydrating its Cys179 to prevent the activation of the NF-\kappa B pathway and subsequently control the inflammation of pulmonary artery endothelial cells in PH [39]. In addition, H\textsubscript{2}S controlled MCT-induced PH in rats by inhibiting the aggregation and degranulation of mast cells and the release of interleukin-6 [41]. Endothelial-to-mesenchymal transition (EndMT) plays an important role in PH. The investigators indicated a beneficial effect of H\textsubscript{2}S on PH development via inhibiting the NF-\kappa B pathway and the subsequent pulmonary artery EndMT [40].

5. Role of H\textsubscript{2}S in High Pulmonary Blood Flow-Induced PH

High pulmonary blood flow-induced PH is a common complication of CHD in patients with a left-to-right shunt [42]. The severity of PH progression closely affects the timing of surgeries, their success rate, and post-operative prognosis. In experimental studies on rats, an animal model of high pulmonary blood flow-induced PH was successfully developed by performing an experimental operation to create an abdominal aorta/inferior vena cava shunt. Li et al. [43,44] reported that the H\textsubscript{2}S/CSE pathway of the lung tissue in rats was increased following 4 weeks of shunting. However, the H\textsubscript{2}S/CSE of the lung tissues of shunt rats after 11 weeks was downregulated. At the same time, PASP was markedly raised, and pulmonary vascular structural remodeling developed in the shunt rats. After exogenous H\textsubscript{2}S donor supplementation in shunt rats, the pulmonary vascular remodeling was reduced, and the PASP was successfully decreased.

We showed that H\textsubscript{2}S played its regulatory role in PH induced by increased pulmonary blood flow via several mechanisms [42–47]. In one study, H\textsubscript{2}S inhibited the proliferation of PASMCs through mitogen-activated protein kinase/extracellular signal-regulated kinase signaling to alleviate the pulmonary vascular structural remodeling and PH induced by high pulmonary blood flow in rat models [44]. In addition, it inhibited the pulmonary
artery inflammatory response of rats with increased pulmonary blood flow, via downregulation of the NF-kB pathway. Other studies also showed that H₂S promoted collagen degradation in the pulmonary artery walls and reduced the accumulation of ECM in the pulmonary vascular structural remodeling and PH caused by increased pulmonary blood flow [17,45]. Interestingly, these studies showed that H₂S regulated the production of vasoactive peptides, such as endothelin-1 (ET-1), atrial natriuretic peptide (ANP), calcitonin gene-related peptide (CGRP), and pro-adrenomedullin peptide (PAMP) to regulate the pulmonary hemodynamics and structure [48]. Furthermore, it inhibited the production of endogenous vasoconstrictors, such as ET-1, ANP, and CGRP but promoted the plasma vasoactive PAMP levels to relax blood vessels and relieve PH [48].

Of note, the interaction between H₂S/CSE and NO/nitric oxide synthase (NOS) pathways was involved in the development of high pulmonary blood flow-induced pulmonary vascular structural remodeling and PH. Wang et al. found that after 11 weeks of abdominal aorta-inferior cava vein shunting operation, high pulmonary blood flow-induced pulmonary vascular structural remodeling and PH developed in association with a down-regulated H₂S/CSE pathway. While, for shunt rats administrated with L-arginine, a substrate of NOS, the H₂S/CSE pathway was markedly upregulated in the shunt rats with L-arginine treatment, and at the same time, the pulmonary artery pressure was significantly decreased in comparison to those in the shunt rats without L-arginine treatment. The above results suggested that the upregulated endogenous H₂S might partly contribute to the inhibitory effect of L-arginine on the high blood flow-induced PH [42].

6. Role of H₂S in PH Associated with CHD

PH is a common complication of CHD [49]. Sun et al. [49] reported that decreased H₂S and increased Hcy concentrations were correlated with PH in patients with CHD. The study indicated that the plasma Hcy contents and the H₂S concentration yielded good sensitivity and specificity to predict obstructive PH in CHD cases, respectively, indicating that Hcy and H₂S are potential diagnostic biomarkers. Tan et al. [50] also reported that H₂S levels have an important predictive value for the prognosis of CHD. They showed that the endogenous H₂S concentration was negatively correlated with the mechanical ventilation duration, duration of stay in ICU, and maximum vasoactive drug scoring value at 24 and 48 h following cardiac surgery, respectively. The results suggested that the endogenous H₂S levels had a potential clinical significance in the prediction of the prognosis of CHD cases after cardiac surgery.

7. Conclusions and Perspectives

Endogenous H₂S as a third gaseous molecule plays a crucial part in the pathophysiology responsible for PH. H₂S attenuates the vascular endothelial cell inflammatory response, inhibits PASMC proliferation, modulates vascular cell apoptosis and inhibits collagen remodeling, opens the KₐTP channel to relax pulmonary vessels [11,17,18], and interacts with CO and NO signaling pathways to exert vascular function and maintain normal pulmonary circulation [19]. Under certain pathologic stimuli, the endogenous H₂S pathway is downregulated, thus inducing the development of PH.

Further understanding the involvement of the H₂S pathway and the molecular mechanisms underlying the development of PH, as well as its vascular function regarding the pulmonary vessels, would attract great interest for the exploration of novel potential therapeutic targets of PH in future studies. The studies show that H₂S plays a protective part in the development of PH and might be a target for a new treatment strategy with H₂S-releasing molecules [51]. The potential therapeutic effect is mainly established in H₂S supplementation experiments using H₂S donors. The most widely used H₂S donors are NaHS and Na₂S [19,51–55]. They have several advantages, such as being inexpensive, water-soluble, and having the ability to rapidly release a large amount of H₂S under physiological conditions. While GYY4137 or dithiolthione compounds work as slow-releasing H₂S donors, are actively developed, and exhibit promising effects on
cardiovascular diseases [19,56,57], some other H$_2$S donors have been demonstrated to protect against cardiac dysfunction, vascular remodeling, and PH. Recently, investigators have revealed that the designed microfluidics-assisted H$_2$S-releasing aspirin derivative (ACS14)-containing large porous microspheres showed promising potential as an inhaled and efficacious H$_2$S donor in treating MCT-induced PH [58]. In addition, a variety of H$_2$S donors have been developed. Naturally occurring donors include diallyl sulfide, diallyl disulfide, and diallyl trisulfide, while synthetic H$_2$S donors consist of the following kinds: hydrolysis-triggered donors consisting of Lawesson’s reagent and derivatives, as well as dithiothiones; thiol-triggered donors comprised of N-benzylothiobenzamides, acyl perthiols, dithioperoxanhydrides, polysulfides, arylthioamides, and S-aryloxythiooximes; light-triggered donors which include geminal-dithiols, ketoprofenate photocages, and α-thioetherketones; enzyme-triggered donors; and finally, dual carbonyl sulfide/H$_2$S donors consisting of N-thiocarboxyanhydrides and self-immolative thiocarbamates [56]. The clinical significance of H$_2$S clinical translation and its donor discoveries in the treatment of PH merit interdisciplinary studies.

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**Abbreviations**

ANP: atrial natriuretic peptide; CHD: congenital heart disease; CGRP: calcitonin gene-related peptide; CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; CSE: cystathionine-γ-lyase; ECM: extracellular matrix; EndMT: Endothelial-to-mesenchymal transition; ET-1: endothelin-1; MCT: monocrotaline; H$_2$S: hydrogen sulfide; Hcy: homocysteine; HO: heme oxygenase; HPH: hypoxic pulmonary hypertension; IKKβ: inhibitor of κB kinase subunit β; NF-κB: nuclear factor kappa B; NO: nitric oxide; NOX4: nicotinamide adenine dinucleotide phosphate oxidase 4; PAMP: pro-adrenomedullin peptide; PAP: pulmonary artery pressure; PASMC: pulmonary artery smooth muscle cell; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; PGI2: prostaglandin; ROS: reactive oxygen species; SO$_2$: sulfur dioxide; VSMC: vascular smooth muscle cell.

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