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MINIREVIEWS

Role of hydrogen sulphide in airways

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Abstract

The toxicity of hydrogen sulfide (H_2S) has been known for a long time, as it is prevalent in the atmosphere. However accumulative data suggest that H_2S is also endogenously produced in mammals, including man, and is the third important gas signaling molecule, besides nitric oxide and carbon monoxide. H_2S can be produced *via* non enzymatic pathways, but is mainly synthesized from L-cysteine by the enzymes cystathionine-γ-lyase, cystathionine-β-synthetase, cysteine amino transferase and 3-mercaptopyruvate sulfurtransferase (3MTS). The formation of H_2S from D-cysteine *via* the enzyme D-amino acid oxidase and 3MTS has also been described. Endogenous H_2S not only participates in the regulation of physiological functions of the respiratory system, but also seems to contribute to the pathophysiology of airway diseases such as chronic obstructive pulmonary disease, asthma and pulmonary fibrosis, as well as in inflammation, suggesting its possible use as a biomarker for these diseases. This review summarizes the different implications of hydrogen sulfide in the physiology of airways and the pathophysiology of airway diseases.

Key words: Hydrogen sulfide; Airways; Asthma; Chronic obstructive pulmonary disease; Inflammation

Core tip: Hydrogen sulfide (H_2S) is a metabolite produced in mammalian organisms both in physiological and in pathological conditions. The measured levels appear differentiated in inflammatory airway diseases, showing the need to acknowledge H_2S not only as a metabolic mediator but as a signaling biomarker as well. This could be of clinical importance since H_2S levels could be used in order to access staging or treatment efficiency in patients suffering from airway diseases.

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INTRODUCTION

Hydrogen sulfide (H_2S) is prevalent in the atmosphere since it is generated from sources both manmade and natural. Therefore organisms may need to either

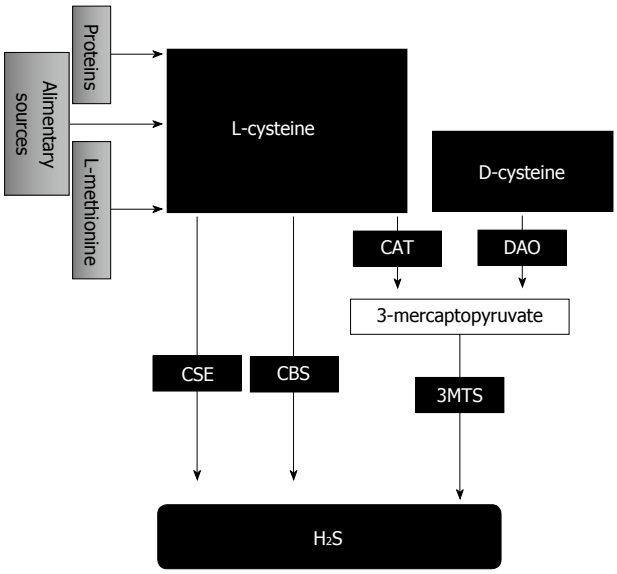

Figure 1 Schematic presentation of pathways for hydrogen sulfide synthesis from L- and D-cysteine *via* the enzymes cystathionine-γ-lyase, cystathionine-β-synthetase, cysteine amino transferase, D-amino acid oxidase and 3-mercaptopyruvate sulfurtransferase. H_2S: Hydrogen sulfide; CSE: Cystathionine-γ-lyase; CBS: Cystathionine-β-synthetase; CAT: Cysteine amino transferase; DAO: D-amino acidoxidase; 3MTS: 3-mercaptopyruvate sulfurtransferase.

protect themselves from H_2S or respond to it, but not particularly in a true signaling way. Although its production in mammalian tissues has been long known, H_2S was largely ignored as a metabolic waste. Its toxicity seems to depend mainly on the concentration and considerably less on the duration of H_2S exposure[1]. Importantly, accumulating data suggest that H_2S is indeed endogenously produced in mammals, including man, and it represents the third important gas-signaling molecule, besides nitric oxide (NO) and carbon monoxide (CO). Even more, a possible interaction between gas-signaling molecules, especially NO and H_2S, has been described[2,3]. Endogenously produced H_2S affects many biological processes in most human systems, including gastrointestinal, cardiovascular, nervous, endocrine system and kidneys[4-6]. Available data suggest that main cellular targets of H_2S are ion channels, such as ATP-sensitive potassium channels (K_{ATP}) and transient receptor potential vanilloid channels (TRPV)[7], transcription factors, such as heme oxygenase-1 (HO-1) and nuclear factor kappa B (NF-κB)[8,9], as well as kinases like mitogen-activated protein kinases (MAPK)[10]. These biological effects of H_2S have led to the study of its implication in many diseases and the development of H_2S-donating drugs with a possible clinical potential[6,11]. The involvement of H_2S in the early stages as well as in the development of inflammatory diseases of the respiratory system makes it important to identify it as a biomarker that could be helpful in the prediction or the treatment of such pathological conditions. This review focuses on the effects of H_2S on the respiratory system and its implication in airway diseases.

H_2S METABOLISM

The metabolic pathways of H_2S production in mammals, have been extensively described and are summarized elsewhere[11-13]. Briefly, H_2S can be synthesized from L-cysteine, a sulfur-containing amino acid derived from alimentary sources, synthesized from L-methionine through the so-called "trans-sulfuration pathway" with homocysteine as an intermediate, or released from endogenous proteins[1] (Figure 1). H_2S is synthesized from L-cysteine by the enzymes cystathionine-γ-lyase (CSE) and cystathionine-β-synthetase (CBS). These enzymes are responsible for the majority of the endogenous production of H_2S and their expression appears to be tissue specific[14]. Furthermore, the enzyme cysteine amino transferase (CAT) catalyzes the formation of 3-mercaptopyruvate from L-cysteine that is converted to H_2S by the enzyme 3-mercaptopyruvate sulfurtransferase (3MTS). H_2S can also be synthesized from D-cysteine *via* the enzyme D-amino acidoxidase (DAO) that converts D-cysteine to 3-mercaptopyruvate, followed by its conversion to H_2S by 3MTS[13]. H_2S can also be produced *via* non enzymatic pathways but these pathways account only for a small portion of the total H_2S production[5].

H_2S, once produced in mammalian cells, can be stored as bound sulfane sulphur and released later in response to a physiological stimulus[12]. H_2S is removed quickly from the cellular environment *via* three main catabolic pathways: (1) H_2S oxidation, which takes place mainly in mitochondria, initially to thiosulfate, followed by its conversion to sulfite and sulfate; (2) H_2S methylation by thiol S-methyltransferase (TSMT) to methanethiol and dimethylsulfide; and (3) sulfhemoglobin formation by H_2S binding to methemoglobin[7] (Figure 2).

H_2S EFFECT ON AIRWAYS PHYSIOLOGY

Many different methods have been used in order to estimate H_2S physiological levels in the plasma or validate its use as a biomarker for a variety of pathophysiological conditions. This effort is not always easy, due to artifacts, which often lead to inconsistent and contradicting measurements[15]. However, there are studies showing that in healthy adults between the age of 56.6 to 75.0 years, the median H_2S serum concentration is approximately 35 μmol/L[16], while H_2S plasma concentration seems to be higher in 6-12 years old children (Table 1)[17]. H_2S concentration in exhaled air of healthy adult subjects was found to be 8-16 ppb[18]. On the other hand, H_2S concentration in lungs, at least in rat, is approximately 30 μmol/L[19]. H_2S levels appear altered in some pathological conditions of the airways, like asthma, Chronic Obstructive

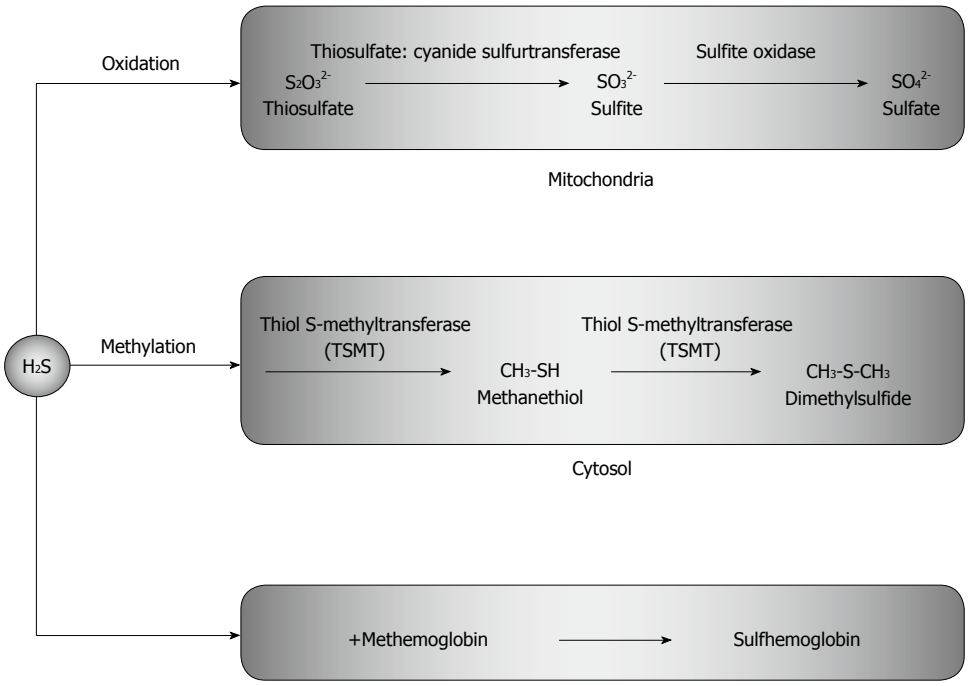

Figure 2 Main catabolic pathways of hydrogen sulfide. H_2S: Hydrogen sulfide.

Table 1 Hydrogen sulfide concentration in healthy subjects and patients with asthma, chronic obstructive pulmonary disease or pneumonia

Subjects	Age (yr)	H_2S concentration in serum/plasma (μmol/L)	Ref.
Healthy			
	71-80	35.7 ± 1.2	[16]
	61-70	34.0 ± 0.9	[16]
	50-60	36.4 ± 1.1	[16]
	64.1 ± 8.7	35.4 ± 5.3	[43]
	9.22 ± 1.80	52.60 ± 5.56	[17]
Patients with bronchial asthma			
Bronchial asthma	6-12	44.17 ± 10.95	[17]
Neutrophilic group	53.0 ± 13.9	8.8 ± 4.7	[46]
Paucigranulocytic group	45.5 ± 15.7	6.9 ± 2.0	[46]
	9.03 ± 1.84	44.17 ± 10.95	[17]
Patients with stable COPD			
Patients with acute exacerbations of COPD			
	73.9 ± 8.3	33.8 ± 18.6	[43]
Patients in stage Ⅰ to Ⅱ	65.6 ± 1.6	40.5 ± 6.3	[16]
Patients in stage Ⅲ		33.4 ± 2.9	[16]
Patients in stage Ⅳ		27.6 ± 1.6	[16]
Patients with pneumonia	57.6 ± 20.4	22.7 ± 14.6	[43]
		H_2S concentration in exhaled air (ppb)	
Healthy	52.86 ± 19.81	8.0-16.0	[18]
Patients with bronchial asthma			
Eosinophilic group	46.0 ± 15.2	7.7 ± 4.2	[46]
Paucigranulocytic group	45.5 ± 15.7	11.1 ± 4.6	[46]
Patients with COPD			
Acute exacerbations	67.5 ± 11.47	8.0-13.0	[18]
Stable COPD	64.11 ± 8.79	9.0-12.0	[18]

H_2S: Hydrogen sulfide; COPD: Chronic Obstructive Pulmonary Disease.

Pulmonary Disease (COPD) and pneumonia (Table 1) suggesting that H_2S is probably involved in the pathophysiology of some airways diseases. Therefore, like exhaled NO, H_2S may be a possible biomarker for pulmonary diseases and/or a potential target for new therapeutic approaches for these diseases. Recent studies suggest that H_2S participates in the relaxation of airway smooth muscle (Table 2). As far as the ability of airways to produce H_2S is concerned, it has only been showed in porcine airways that H_2S can be produced endogenously and that the H_2S precursor, L-cysteine caused a concentration-dependent relaxation in peripheral bronchioles[20]. Most of the studies concerning the effect of H_2S on airways are focused on the effect of exogenous H_2S, using H_2S donors. Contractility studies regarding the effect of the rapidly releasing H_2S donor, sodium hydrosulfide (NaHS) demonstrated that H_2S caused a concentration-dependent relaxation in porcine[20], mouse and guinea pig bronchi[21], as well as in rat trachea[22]. This relaxant effect did not depend on epithelium integrity, K_{ATP} channels opening or NO release[22]. On the other hand, in guinea pig bronchi[23], as well as mice lung[24], H_2S seems to induce the release of sensory neuropeptides, due to the activation of TRPV1 receptors, resulting to the contraction of these bronchi. Therefore, when sensory nerves were desensitized by capsaicin treatment, H_2S induced a slight relaxation[23]. Deviations from these findings emerged from the study of Kubo *et al*[21], which showed that NaHS did not cause contraction in guinea pig bronchi, but a slight relaxation. Recently, an *in vivo* study revealed that

Table 2 The effect of hydrogen sulfide on airway smooth muscle function

Tissue	H_2S effects	Involved mechanism	Ref.
Porcine peripheral bronchiols	Relaxation	Alteration in K^+ channels activity	[20]
Guinea pig main bronchus	Slight relaxation		[21]
Guinea pig airways	Neurogenic inflammatory responses	Stimulation of TRPV1 receptors on sensory nerves endings	[23]
Mouse main bronchus	Relaxation	Independent of NK_1/NK_2 tachykinin receptors, K_{ATP} channels, production of NO, cGMP and prostaglandins	[21]
Mouse lung	Neurogenic inflammation	Stimulation of NK_1 and Substance P release	[24]
Mouse small intrapulmonary airways	Relaxation	Inhibition of Ca^{2+} release from intracellular stores through $InsP_3$ receptors	[27]
Mouse tracheal smooth muscle cells	Relaxation	Activation of BK_{Ca} channels	[26]
Rat trachea	Relaxation	Independent of K_{ATP} channels, β-adrenoceptors, epithelium and production of NO, cGMP and prostaglandins	[22]
Human ASMCs	Relaxation	Opening of K_{ATP} channels	[29]
Isolated human airway smooth muscle cells	Relaxation Decrease of cell proliferation and IL-8 release	Inhibition of ERK-1/2 and p38 MAPK phosphorylation	[30]

H_2S: Hydrogen sulfide; TRPV: Transient receptor potential vanilloid channels.

Table 3 Implication of hydrogen sulfide in the pathophysiology in human airway diseases - its use as a biomarker

Disease	
COPD	Higher serum H_2S level in patients with COPD compared with healthy subjects[16]
	Acute exacerbation of COPD decreases serum H_2S level compared to patients with stable COPD[16,42]
	Higher sputum H_2S levels in patients with acute exacerbation of COPD compared to those with stable COPD[42]
	Higher sputum-to-serum ratio of H_2S in COPD subjects with acute exacerbation comparative with those with stable disease[42]
	Lower serum H_2S levels in patients with COPD who required antibiotics treatment[43]
Asthma	In children, serum H_2S concentration was significantly decreased compared to healthy subjects and correlated positively with FEV_1[17]
	In adults, exhaled H_2S was lowest in eosinophilic asthma correlated positively with FEV_1[46]
Pulmonary fibrosis	H_2S suppress human fibroblast migration, proliferation and phenotype transform stimulated by fetal bovine serum and growth factors and inhibits the TGF-$β_1$-induced differentiation of fibroblasts to myofibroblasts[53]

H_2S: Hydrogen sulfide; COPD: Chronic Obstructive Pulmonary Disease; FEV_1: Forced expiratory volume during first second; TGF-$β_1$: Transforming growth factor beta 1.

NaHS treatment inhibited the ozone-induced bronchial hyperresponsiveness in mice[25]. Studies regarding the mechanisms involved in H_2S-induced relaxation of airways showed that H_2S exerts its effect mainly by decreasing intracellular calcium levels. This is due both to reduced calcium influx[26] and to inhibition of Ca^{2+} release from intracellular stores through $InsP_3$ receptors[27].

It has also been shown, that H_2S is involved in the relaxation of different smooth muscle types, by affecting a variety of ion channels. For example, in vessels, H_2S induces smooth muscle relaxation *via* its effect on K_{ATP} channels located on vascular smooth muscle cells, or on small to medium conductance K^+ channels located on vascular endothelial cells, which results to membrane hyperpolarization and smooth muscle relaxation[28]. Similarly, in airways, evidence suggests the implication of K^+ channels in the relaxant effect of H_2S[20]. Moreover, in primary cultured mouse tracheal smooth muscle cells NaHS seems to activate large conductance calcium activated potassium channels (BK_{Ca}) causing an increase in potassium outward currents, cell hyperpolarization and inhibition of Ca^{2+} influx[26]. Furthermore, H_2S caused relaxation by opening K_{ATP} channels in isolated human airway smooth muscle cells[29].

Finally, both endogenous and exogenous H_2S decreased human airway smooth muscle cell proliferation and interleukin (IL)-8 release induced by FCS, *via* the inhibition of the phosphorylation of extracellular signal-regulated kinase (ERK)-1/2 and p38 MAPK[30]. The effects of H_2S donors that have been described were not affected by the inhibition of CSE, the blockade of K_{ATP} channels or NO production.

H_2S IN THE PATHOPHYSIOLOGY OF AIRWAY DISEASES

Endogenous H_2S participates in the regulation of physiological functions of the respiratory system (Table 3) and seems also to contribute in the pathophysiology of airway diseases such as COPD, asthma and pulmonary fibrosis (Table 3), suggesting its possible use as a biomarker for these diseases. Apart from the specific features of the pathophysiology, inflammation is a common theme of these diseases. Over the past decade, research data support a key role for H_2S in acute or chronic inflammation in different

clinical conditions[31] and suggest that H_2S has anti-inflammatory and cytoprotective effects that could be beneficial in lung diseases. Animal studies suggest that H_2S in the lung increases the anti-inflammatory cytokine, IL-10, while it decreases the pro-inflammatory cytokine, IL-1β in burn and smoke-induced acute lung injury murine models[32] or hyperoxia-induced acute lung injury models in mice[33]. Animal studies also revealed that treatment with H_2S attenuated lung injury and prolonged the subjects' survival[32,33]. Similarly, inhalation of H_2S appears to be protective against ventilator-induced lung injury, in mice, by limiting cytokine release and neutrophil transmigration[34]. This protective role is associated with down-regulation of genes related to oxidative stress and inflammation and up-regulation of anti-apoptotic and anti-inflammatory genes[35]. Activating transcription factor 3 (Atf3), a protein that limits pro-inflammatory cytokine expression and controls the balance between proliferative and apoptotic signals[36,37], may have an important role in H_2S mediated lung protection, since H_2S inhalation up-regulated *Atf3* gene[35]. Finally, in mice, NaHS treatment reduced the ozone-induced increase of the total cell number, including neutrophils and macrophages; the levels of cytokines, including tumor necrosis factor-α (TNF-α), chemokine ligand 1, IL-6 and IL-1β[25], as well as the increase of the bronchial alveolar lavage (BAL) fluid. On the other hand, inhalation of H_2S protects against ventilator-induced lung injury by preventing edema formation, apoptosis, proinflammatory cytokine production, neutrophil accumulation, and inhibits heme oxygenase-1 expression[34].

Although most of the studies suggest that H_2S has an anti-inflammatory role, some studies have showed that it may contribute to neurogenic inflammation in airways[38]. Thus, both in guinea pig[23] and mouse[24] H_2S induced the release of sensory neuropeptides, while only in mice, it also affected the level of substance P in the lungs, in sepsis-associated lung injury[39].

COPD

Despite inflammation, smoking is the main contributory factor for developing this disease. Animal studies suggest that H_2S is protective against smoking-induced lung injury. Namely, exposure of rats to cigarette smoke resulted to an increase in CSE levels and the subsequent H_2S administration reduced the number of inflammatory cells, as well as airway hyperresponsiveness[40]. Similar findings were reported in mice with tobacco smoke-induced emphysema[41]. Clinical studies showed evidence that H_2S may be implicated in the pathophysiology of COPD and alteration of its levels may be connected with the severity of the disease. In humans, H_2S serum levels were significantly higher in patients with COPD compared to healthy subjects and a positive correlation between the severity of COPD and H_2S serum levels has been shown. Namely, in patients with stable COPD, H_2S serum levels were lower in patients with stage Ⅲ than in those with stage Ⅰ obstruction. Additionally, in patients either with or without COPD H_2S correlated positively with the percentage of predicted forced expiratory volume (FEV_1)[16]. On the other hand, acute exacerbation of COPD decreases H_2S serum levels compared to those of patients with stable COPD[16,42]. On the contrary, H_2S sputum levels were significantly higher in patients with acute exacerbation of COPD compared to those with stable COPD, which resulted in a higher sputum-to-serum level ratio of H_2S in COPD subjects with acute exacerbation in comparison to those with stable disease[42]. As far as COPD treatment is concerned, measured H_2S serum levels were significantly lower in patients with COPD who required antibiotics treatment[43], while theophylline treatment did not alter significantly H_2S serum levels of COPD patients[44].

Asthma

Clinical studies indicate that H_2S serum levels were decreased in patients with either stable asthma or severe acute exacerbations. Even more the changes in H_2S serum[45] or exhaled air[25] levels correlated positively with FEV_1 and negatively with the count of sputum cells, neutrophils[46] or eosinophils[25]. Similarly in children with asthma, H_2S serum concentration was significantly decreased compared to healthy children and the concentration was positively correlated with lung function indices[17]. Whether the decrease of H_2S serum levels in patients suffering from asthma is the cause or the consequence is not yet clear. Therefore, it is not clear if H_2S levels could be used as a biomarker for the disease, like exhaled NO. However, Tian *et al*[17] proposed that decreased H_2S serum levels might be used to indicate decreasing lung function and Wang *et al*[45] suggested that nasal H_2S could be a way of accurately detecting H_2S metabolism in the respiratory system since its levels will not be affected by oral conditions.

Additional evidence for the possible implication of H_2S in the pathophysiology of asthma comes from animal studies. In the lungs of OVA-treated rats with asthma H_2S serum levels and H_2S production from the lungs were decreased in correlation with the decreased CSE expression level and CSE activity in lung tissues[47]. Even more the administration of NaHS or the CSE blocker, D,L-propargylglycine, alleviated or aggravated, respectively, airway hyper-responsiveness in both cigarette smoke exposure model and OVA-induced asthma rat models[40,47].

Pulmonary fibrosis

Pulmonary fibrosis is the final common pathway of a diverse group of lung disorders and is characterized by accumulation and abnormal activation of fibroblasts and myofibroblasts, resulting in excess extracellular matrix deposition and alveolar disruption[48]. Idiopathic pulmonary fibrosis (IPF) is caused by unknown reasons

and its pathophysiology has not yet been clarified, while there is a controversy among researchers whether inflammation constitutes the initial stimulus. Nevertheless, the initial stage is quickly followed by abnormal wound healing[49] and the main protein involved in this process seems to be epithelial cell-derived transforming growth factor beta 1 (TGF-β_1)[50,51]. Evidence suggests that the endogenous CSE/H_2S pathway may participate in the pathogenetic process of pulmonary fibrosis. Myofibroblasts have a main role in the pathogenesis of this disease and although they are generally considered to be differentiated from existing interstitial fibroblasts or bone marrow-derived stem/progenitor cells, epithelial cells also seem to be an important source of myofibroblasts in pulmonary fibrosis[25]. H_2S seems to facilitate the maintenance of alveolar epithelial cell phenotype, since TGF-β_1 induces epithelial–mesenchymal transition and this effect is suppressed by H_2S through a decrease in Smad2/3 phosphorylation, in lungs[52]. Fang *et al*[53] reported that H_2S suppressed human fibroblast migration, proliferation and phenotype transform that was stimulated by fetal bovine serum and growth factors and more specifically inhibited the TGF-β_1-induced differentiation to myofibroblasts. These effects on pulmonary fibroblasts were partially mediated by decreased phosphorylation of ERK. Animal studies showed that NaHS administration ameliorated the bleomycin induced pulmonary fibrosis in rats[54,55]. This protective effect of H_2S is due, partly, to inhibition of NF-κB p65 expression and regulation of Th1/Th2 balance[55].

Last but not least it is important to point out the potential therapeutic use of H_2S. Studies show that both the metabolite itself and its donors could be potentially used in the treatment of various diseases. Specifically, the H_2S donor GYY4137 exhibits antihypertensive activity[1], while other donors have anti-inflammatory[56] and antioxidant properties[57]. As far as respiratory diseases are concerned, there are studies showing that the donor-induced elevated levels of H_2S are useful in the treatment of respiratory distress syndrome as well as other pathological conditions, since H_2S can reduce the oxidative stress that is present in such disorders[1].

CONCLUSION

H_2S appears to play a role both in the physiological function and the pathobiological conditions of the respiratory system. Its presence as a metabolite in inflammatory diseases, as well as the correlation that is found between H_2S and inflammation mediators such as cytokines or growth factors, support its use as a biomarker of pathological conditions in both the lungs and the airways. However, determining H_2S levels in body fluids is not an easy task, because H_2S levels are influenced by H_2S inhaled from atmospheric air. Such artifacts make its use as a biomarker difficult. Therefore, further studies are required in order to determine the physiological H_2S levels and their correlation with the phase, arising or deteriorating, of inflammatory diseases. Overall, it seems that H_2S is not a cell waste, but an important metabolite that has yet to receive the proper attention.

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