Hydrogen Sulfide in Airway Diseases

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Min Review

Hydrogen Sulfide (H\textsubscript{2}S) is a colorless, water-soluble gas with the odor of rotten eggs. H\textsubscript{2}S can be produced via non-enzymatic pathways, but is mainly synthesized from L-cysteine as the substrate by Cystathionine-γ-lyase (CSE), Cystathionine-β-synthetase (CBS) and 3-mercaptopyruvate sulfur transferase (3MTS).\textsuperscript{1} H\textsubscript{2}S is now recognized as the third signaling gasotransmitter after Carbon monoxide (CO) and Nitric Oxide (NO), and it plays an important role in the pathophysiology of airway disease, such as asthma and Chronic Obstructive Pulmonary Disease (COPD).\textsuperscript{1}

H\textsubscript{2}S AND ASTHMA

Asthma is a chronic airway disorder characterized as airway inflammation, airway hyper responsiveness (AHR), and airway remodeling, which is caused by inflammatory cells such as eosinophils, mast cells, T-helper 2 (Th2) lymphocytes, neutrophils, and structural cells such as airway epithelial cells and airway smooth muscle cells (ASMCs). The levels of H\textsubscript{2}S in serum were decreased in patients with stable asthma or acute exacerbation asthma.\textsuperscript{2} The changes in serum H\textsubscript{2}S levels or exhaled air were positively correlated with FEV\textsubscript{1} and negatively with the total count of sputum cells and neutrophils percentage.\textsuperscript{2,3} Similar findings were observed in pediatric asthmatics. The serum levels of H\textsubscript{2}S were significantly decreased in asthmatic children compared to healthy children and the levels were positively correlated with lung function.\textsuperscript{4} Therefore, it was proposed that H\textsubscript{2}S level could be used as a biomarker for asthma.\textsuperscript{5}

Animal studies showed that the serum H\textsubscript{2}S level, the production rate of H\textsubscript{2}S in lung tissue, and the expression of CSE were decreased in an Ovalbumin (OVA)-induced rat model of asthma.\textsuperscript{6,7}

Exogenous supplementation with Sodium Hydrogen Sulfide (NaHS, an exogenous donor of H\textsubscript{2}S) improved the airway flow and attenuated airway inflammation and remodeling in the model,\textsuperscript{6} while inhibition in the synthesis of H\textsubscript{2}S aggravated the development of airway inflammation and AHR.\textsuperscript{7}

H\textsubscript{2}S AND COPD

Chronic Obstructive Pulmonary Disease (COPD) is a chronic airway disease characterized by chronic inflammation and parenchymal destruction (emphysema), which ultimately contributes to irreversible airflow obstruction. Cigarette Smoke (CS) or other noxious particles are the main etiologic factors for the development of COPD. A clinical study investigating the relation of serum H\textsubscript{2}S levels to the severity of COPD showed that serum H\textsubscript{2}S levels were significantly higher in patients with stable COPD than in patients with Acute Exacerbation of COPD (AECOPD) and control subjects. Serum H\textsubscript{2}S levels were positively correlated with the percentage of predicted FEV\textsubscript{1} value, and negatively correlated with the proportion of neutrophils in sputum in all patients.\textsuperscript{8} This study indicated that H\textsubscript{2}S may be involved in the pathogenesis of airflow obstruction in COPD and may be connected with disease activity and severity. Moreover, sputum H\textsubscript{2}S levels were higher in AECOPD patients than those in stable COPD patients. Thus, the high sputum-to-serum ratio of H\textsubscript{2}S may indicate an ongoing neutrophilic inflammation.\textsuperscript{8}

Citation

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The important role of H₂S in COPD was further confirmed through animal studies. Han, et al. showed that chronic CS could down-regulate the expression of CSE and CBS in the rat lung, while treatment with NaHS could inhibit both airway inflammation and airway remodeling as well as attenuate the development of emphysema and pulmonary artery hypertension. Another study showed that the treatment with NaHS reduced the airway inflammation and AHR caused by Cigarette Smoke (CS) while treatment with PPG (the inhibitor of CSE) further aggravated the development of airway inflammation and AHR due to the inhibition of the production of endogenous H₂S.

THE ROLE OF H₂S IN MODULATING AIRWAY DISEASE

Anti-inflammatory

Presently, most studies demonstrate that H₂S possesses an anti-inflammatory function in many models of respiratory disease, including asthma. Although the anti-inflammatory mechanism of H₂S is not clear, the exogenous addition of H₂S could inhibit Th2-cytokines like IL-5 and IL-13 in addition to eotaxin-1 in the BAL fluid in an OVA-induced murine asthma model. Treatment with NaHS could decrease the production of pro-inflammatory cytokines such as IL-6 and IL-8 and increase the production of anti-inflammatory cytokines such as IL-10 in the plasma and lung tissues.

Anti-oxidative

H₂S can freely cross the plasma membrane and the mitochondrial membrane to scavenge Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). Moreover, H₂S enhances the production of reduced Glutathione (GSH) by enhancing cystine/cysteine transporters and redistributes GSH to mitochondria. NaHS increased the ratio of reduced/oxidized glutathione (GSH/GSSG) and decreased the content of 8-hydroxy-deoxyguanosine (8-OHdG) in the lungs of CS-exposed mice, which was similar to our findings that NaHS inhibited ozone-induced oxidative stress in a murine model. Benetti, et al. confirmed that NaHS treatment abolished the increased lipid peroxidation in the allergic mouse lungs and increased Superoxide dismutase (SOD), Glutathione peroxidase (GPx) and Glutathione Reductase (GR) enzyme activities. Nuclear factor (erythroid-derived 2)-like 2, also known as Nrf2, is a key transcription factor that regulates the expression of many important antioxidant proteins that protect against oxidative damage triggered by injury and inflammation.

Regulation of Cell Proliferation and Apoptosis

H₂S can inhibit cell proliferation; however, the effects of H₂S on cellular apoptosis are complex. An in vitro study showed that both NaHS (the fast-releasing H₂S donor) and GYY4137 (the slow-releasing H₂S donor) suppressed human Airway Smooth Muscle Cell (ASMC) proliferation induced by Fetal Bovine Serum (FBS) and the proinflammatory cytokines IL-1β and IL-8. H₂S decreased the migration and proliferation of a human lung fibroblast cell line (MRC5) stimulated by FBS and basic Fibroblast Growth Factor (bFGF), which is probably related to the fact that H₂S inhibits ERK-1/2 phosphorylation in MRC5 cells.

Inhibitory Effect on AHR

Animal experiments showed that NaHS reduced the AHR caused by OVA, ozone, and cigarette smoke, while treatment with PPG aggravated the development of AHR. The underlying mechanism may be related to the direct relaxant effect on bronchial smooth muscle as well as anti-inflammatory and anti-oxidative effects of NaHS. Kube, et al. found that NaHS relaxed the carbachol-precontracted mouse bronchial rings, and this relaxant effect was not affected. The mechanism may be due to that NaHS activates large conductance Calcium activated potassium channels (BKCa) or activates K (ATP) channels in airway smooth muscle cells.

Inhibitory Effect on Airway Remodeling

NaHS inhibited goblet cell hyperplasia, airway mucus secretion, collagen deposition, and subepithelial fibrosis in an OVA-induced rat asthma model. NaHS also inhibited increases in bronchial thickness in a CS-induced mouse emphysema model. NaHS reduces increases in right ventricular systolic pressure, the thickness of pulmonary vascular walls, and the ratio of right ventricle/left ventricle + septum in a CS-induced mouse emphysema model. The inhibitory effect on vascular remodeling by H₂S may be related to the roles of H₂S in promoting the apoptosis of pulmonary artery SMC and in reducing collagen deposition in the pulmonary vasculature.

PERSPECTIVE

H₂S is a novel gas molecule with many biological effects. More research is needed to clarify the metabolism and mechanism of H₂S in airway diseases. Clinical studies have shown that the level of H₂S in plasma, sputum, and exhaled breath could reflect the disease condition and severity of asthma and COPD. Since H₂S plays many roles in airway disease, more focused studies about the effects of H₂S on respiratory protection is urgently needed. Currently, some pharmaceutical companies are developing slow-releasing, controllable H₂S donors and H₂S-releasing hybrid drugs. These drugs may pave new way for the treatment of airway diseases.

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