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Mini Review

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Hydrogen Sulfide in Airway Diseases

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Hydrogen Sulfide (H_2S) is a colorless, water-soluble gas with the odor of rotten eggs. H_2S 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).[1] H_2S 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).[1]

H_2S 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_2S in serum were decreased in patients with stable asthma or acute exacerbation asthma.[2] The changes in serum H_2S levels or exhaled air were positively correlated with FEV_1% and negatively with the total count of sputum cells and neutrophils percentage.[2,3] Similar findings were observed in pediatric asthmatics. The serum levels of H_2S were significantly decreased in asthmatic children compared to healthy children and the levels were positively correlated with lung function.[4] Therefore, it was proposed that H_2S level could be used as a biomarker for asthma.[5]

Animal studies showed that the serum H_2S level, the production rate of H_2S in lung tissue, and the expression of CSE were decreased in an Ovalbumin (OVA)-induced rat model of asthma.[6,7]

Exogenous supplementation with Sodium Hydrogen Sulfide (NaHS, an exogenous donor of H_2S) improved the airway flow and attenuated airway inflammation and remodeling in the model,[6] while inhibition in the synthesis of H_2S aggravated the development of airway inflammation and AHR.[7]

H_2S 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_2S levels to the severity of COPD showed that serum H_2S levels were significantly higher in patients with stable COPD than in patients with Acute Exacerbation of COPD (AECOPD) and control subjects. Serum H_2S levels were positively correlated with the percentage of predicted FEV_1 value, and negatively correlated with the proportion of neutrophils in sputum in all patients.[8] This study indicated that H_2S may be involved in the pathogenesis of airflow obstruction in COPD and may be connected with disease activity and severity. Moreover, sputum H_2S levels were higher in AECOPD patients than those in stable COPD patients. Thus, the high sputum-to-serum ratio of H_2S may indicate an ongoing neutrophilic inflammation.[9]

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The important role of H_2S 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.[10] 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 H_2S.[11]

THE ROLE OF H_2S IN MODULATING AIRWAY DISEASE

Anti-inflammatory

Presently, most studies demonstrate that H_2S possesses an anti-inflammatory function in many models of respiratory disease, including asthma,[6,7] COPD.[10,11] Although the anti-inflammatory mechanism of H_2S is not clear, the exogenous addition of H_2S could inhibit Th2-cytokines like IL-5 and IL-13 in addition toeotaxin-1 in the BAL fluid in an OVA-induced murine asthma model.[7] 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.[12]

Anti-oxidative

H_2S can freely cross the plasma membrane and the mitochondrial membrane to scavenge Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS).[13] Moreover, H_2S enhances the production of reduced Glutathione (GSH) by enhancing cystine/cysteine transporters and redistributes GSH to mitochondria.[14] 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,[10] which was similar to our findings that NaHS inhibited ozone-induced oxidative stress in a murine model.[15] 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.[16] 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

H_2S can inhibit cell proliferation; however, the effects of H_2S on cellular apoptosis are complex. An *in vitro* study showed that both NaHS (the fast-releasing H_2S donor) and GYY4137 (the slow-releasing H_2S donor) suppressed human Airway Smooth Muscle Cell (ASMC) proliferation induced by Fetal Bovine Serum (FBS) and the proinflammatory cytokines IL-1β and IL-8.[17] H_2S 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 H_2S inhibits ERK-1/2 phosphorylation in MRC5 cells.[18]

Inhibitory Effect on AHR

Animal experiments showed that NaHS reduced the AHR caused by OVA,[7] ozone,[19] and cigarette smoke,[11] 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.[20] 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.[21,22]

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.[6] NaHS also inhibited increases in bronchial thickness in a CS-induced mouse emphysema model.[10] 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.[10] The inhibitory effect on vascular remodeling by H_2S may be related to the roles of H_2S in promoting the apoptosis of pulmonary artery SMC,[18] and in reducing collagen deposition in the pulmonary vasculature.[23]

PERSPECTIVE

H_2S is a novel gas molecule with many biological effects. More research is needed to clarify the metabolism and mechanism of H_2S in airway diseases. Clinical studies have shown that the level of H_2S in plasma, sputum, and exhaled breath could reflect the disease condition and severity of asthma or COPD. Since H_2S plays many roles in airway disease, more focused studies about the effects of H_2S on respiratory protection is urgently needed. Currently, some pharmaceutical companies are developing slow-releasing, controllable H_2S donors and H_2S-releasing hybrid drugs. These drugs may pave new way for the treatment of airway diseases.

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