MINI-REVIEW

H₂S as a potential defense against COVID-19?

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Yang G. H₂S as a potential defense against COVID-19? Am J Physiol Cell Physiol 319: C244–C249, 2020. First published June 9, 2020; doi:10.1152/ajp-cell.00187.2020.—The outbreak of COVID-19 pneumonia caused by a new coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) is posing a global health emergency and has led to more than 380,000 deaths worldwide. The cell entry of SARS-CoV-2 depends on two host proteins angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). There is currently no vaccine available and also no effective drug for the treatment of COVID-19. Hydrogen sulfide (H₂S) as a novel gasotransmitter has been shown to protect against lung damage via its anti-inflammation, antioxidative stress, antiviral, prosurvival, and antiaging effects. In light of the research advances on H₂S signaling in biology and medicine, this review proposed H₂S as a potential defense against COVID-19. It is suggested that H₂S may block SARS-CoV-2 entry into host cells by interfering with ACE2 and TMPRSS2, inhibit SARS-CoV-2 replication by attenuating virus assembly/release, and protect SARS-CoV-2-induced lung damage by suppressing immune response and inflammation development. Preclinical studies and clinical trials with slow-releasing H₂S donor(s) or the activators of endogenous H₂S-generating enzymes should be considered as a preventative treatment or therapy for COVID-19.

ACE2; COVID-19; H₂S; SARS-CoV-2; TMPRSS2

INTRODUCTION

In December 2019, a new coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) caused a pneumonia outbreak in Wuhan, China, which is now spreading globally. The World Health Organization declared a Public Health Emergency of International Concern on January 30, 2020. As of June 3, 2020, there has been over 6,519,167 confirmed cases reported with 384,839 deaths worldwide. SARS-CoV-2 is an enveloped nonsegmented positive sense RNA virus, which is ~120 nm in diameter and has 29,903 nucleotides (11, 71). This RNA virus causes an acute respiratory illness of varying severity from the common cold to fatal pneumonia, termed as COVID-19. The patients with preexisting cardiovascular diseases, diabetes, kidney dysfunctions, and cancer, have a higher risk of developing COVID-19 with worse clinical outcomes (16, 24, 40, 46, 73). Aging people are especially vulnerable to this disease, and seniors accounted for more than 80% of all reported COVID-19 deaths in Canada (24, 46). There is currently no vaccine available and also no effective drug for the treatment of COVID-19, and rapid identification of effective ways to combat this new virus is urgently needed.

Hydrogen sulfide (H₂S) is a novel gasotransmitter that plays physiological roles in a variety of functions such as cell survival, energy metabolism, protein modification, and signal transduction (21, 47, 59). The physiological concentration of endogenous H₂S is reported to be in the high nanomolar and low micromolar ranges depending on the tissue and cell types, which is precisely regulated by the endogenous generation and metabolism (8, 59, 72). Three key enzymes, including cystathionine-β-synthase, cystathionine-γ-lyase (CSE), and 3-mercaptopyruvate sulfur transferase, are mostly responsible for the endogenous production of H₂S in mammals, while H₂S can be quickly removed through oxidation, methylation, and/or expiration (10, 72). H₂S has been shown to protect against multiple organ damage via its cardio-protection, anti-inflammation, antioxidant stress, antiviral, and antiaging effects (Fig. 1) (8, 10, 21, 47, 59, 65, 72). This mini-review will focus on H₂S biology and its potential roles in fighting COVID-19.

CAN H₂S BE A STINKY DEFENSE AGAINST SARS-COV-2 VIRUS INFECTION BY BLOCKING ACE2 AND TRANSMEMBRANE PROTEASE SERINE 2?

A spike glycoprotein (S-protein, 1,273 amino acids) expressed on the envelope surface of SARS-CoV-2 is critical for the virus penetration into host cells (56, 64). This S-protein contains two functional domains: a receptor-binding domain in S1 subunit and a putative fusion domain in S2 subunit essential for membrane invasion (64, 71). During viral infection, the two subunits are separated by the host protease, transmembrane protease serine 2 (TMPRSS2). TMPRSS2 along the dibasic
arginine sites (25). S1 subunit is responsible for recognizing and binding to host receptor angiotensin-converting enzyme 2 (ACE2), while the S2 subunit contributes to membrane fusion and viral internalization by endocytosis in human respiratory epithelial cells (Fig. 1) (25, 42). These data suggest that both ACE2 and TMPRSS2 are the keys for SARS-CoV-2 to enter into human cells, and reducing the activities of ACE2 and/or TMPRSS2 may prevent the virus entering the host cell and the spread of infection (42, 67). Indeed, it has been shown that knockout of ACE2 blocked the infection of SARS-CoV-2 into mouse epithelial cells (71). An in vitro study has also confirmed that the entry of SARS-CoV-2 into bronchial epithelial cells could be prevented by a TMPRSS2 inhibitor camostat mesylate (25). The sequence of ACE2 and TMPRSS2 protein among different species, including human, monkey, dog, cat, bovine, and swine, is highly similar, suggesting that SARS-CoV-2 may infect all of these species (14, 36).

ACE2 is a transmembrane protein and is widely expressed in various tissues, including the lung, heart, vasculature, kidney, small intestine, and testis (12, 14, 26, 32). As a key enzymatic component in the renin-angiotensin-aldosterone system (RAAS), ACE2 catalyzes the generation of angiotensin (ANG)-1–7 from ANG II (15, 27). Unlike ACE2, ACE is responsible for the conversion of ANG I to ANG II (15). ACE2 is often reported to be negatively associated with lung injury. ACE2 activity was lower in lipopolysaccharides-induced acute lung injury, and ACE2 knockout mice were more sensitive to acute lung injury compared with normal mice (27, 33). The beneficial effect of ACE2 is mostly due to its effects in reducing ANG II levels followed by improved vasoconstriction, inflammation, cell growth, and tissue remodeling (27, 32). The different regulation of H2S on ACE2 and ACE has been reported. H2S treatment attenuated atherosclerosis in a partially ligated carotid artery mouse model via stimulating ACE2 expression, while an ACE2 inhibitor (MLN-4760) abolished the antiatherosclerotic effect of H2S (38). In contrast, the administration of H2S donor inhibited ACE expression in kidney from spontaneously hypertensive rats and prevented the development of hypertension (52). By blocking ACE/RAAS system, H2S also has been shown to improve endothelial function and myocardial protection.

Fig. 1. The proposed pathways underlying the protective roles of hydrogen sulfide (H2S) against COVID-19. H2S as a novel gasotransmitter regulates a variety of physiological functions and provides protection against organ damages (box 1). H2S also displays beneficial roles in preventing lung disorders (box 2) and viral replication (box 3). Cystathionine-γ-lyase (CSE)-derived H2S (box 4) or exogenously applied H2S may block severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into the host cells by interrupting angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), inhibit virus replication by attenuating syncytium formation and virus assembly/release, and protect SARS-CoV-2-induced lung damage by suppressing the immune response and inflammation development. The dotted line indicates the prediction, and the red line means the blockage of the pathway. CVB3, coxsackie virus B3; PPG, DL-propargylglycine; RSV, respiratory syncytial virus.
mice. It was previously demonstrated that H2S significantly repressed the transcription of TMPRSS2 in epithelium-derived human prostate cancer cells via blocking the binding of transcriptional factor androgen receptor (AR) with androgen-responsive element in TMPRSS2 promoter (70). Further study of these mechanisms suggests that H2S inhibited AR transactivation by blocking AR dimerization (70). It is hypothesized that lower H2S level in various pathological conditions may lead to higher expression of TMPRSS2, which would facilitate the coronavirus entry into cells.

CAN H2S BE A Target FOR INHIBITION OF SARS-COV-2 REPLICATION?

In addition to the possibility of interrupting viral entry, there are some well-established evidence demonstrating that H2S displays a broad inhibitory effect on many highly pathogenic RNA viruses (6, 35). Respiratory syncytial virus (RSV), an enveloped RNA virus, often leads to lower respiratory tract illness and causes higher morbidity and mortality in young children (49). In vitro studies first observed that H2S inhibited viral replication in A549 cells, a human alveolar type II-like epithelial cell line (35). Intranasal delivery of H2S donor TAGDD-1 significantly reduced viral replication in an in vivo mouse model of RSV infection (7). Another H2S donor GYY4137 also resulted in the reduction of RSV titers and improved lung functions in mice (5, 28). In addition, RSV infection led to a lower level of intracellular H2S in airway epithelial cells by inhibiting the expression of CSE (a H2S-generating enzyme) but inducing the expression of sulfide quinone reductase (a H2S-degrading enzyme in mitochondria) (30, 35). In contrast, blockage of CSE activity with Nα-propargylglycine (PPG) resulted in increased viral replication and chemokine secretion (35). Further evidence demonstrated that knockout of CSE gene in mice significantly enhanced RSV-induced lung damage and viral replication compared with wild-type animals (5, 29). The antiviral effect of the H2S donor was often associated with the improved symptoms of less inflammation, oxidative stress, and cellular infiltrates in lung (5, 7).

H2S also has been shown to inhibit the replications of many other RNA viruses in lungs, such as influenza virus, Ebola virus, Nipah virus, human metapneumovirus, Far-eastern subtype tick-borne flavivirus, Rift Valley fever virus, and Crimean-Congo hemorrhagic fever virus (6, 35). Rather than targeting at viral entry into host cells, H2S donor specifically decreased the expression of viral proteins and mRNA and inhibited syncytium formation and virus assembly/release (Fig. 1) (6, 35). In addition, coxsackie virus B3 (CVB3) is a positive-stranded RNA virus, which commonly initiates immune cell infiltration and causes inflammation in the heart, eventually resulting in acute myocarditis and heart failure (60). H2S donors were able to inhibit the inflammatory response in CVB3-induced myocarditis in mice and also CVB3-infected rat cardiomyocytes (60, 69). All these data suggest that H2S would be a potential target for attenuating viral replication, inflammation development, and organ damage, which definitely needs to be further explored in relevant preclinical models of viral infections.

CAN H2S BE A POTENTIAL REMEDY FOR COVID-19 BY REVERSING LUNG DAMAGE?

Accumulated evidence indicated that H2S is essential for normal lung functions, regulating airway tone, epithelial cell survival and death, alveolar development, secretion of extracellular matrix, inflammation, and oxidative stress (13, 23, 31, 43). Endogenously H2S can be mostly generated by CSE with cysteine as the main substrate (58). Lower H2S levels were often observed in lungs when responding to stress conditions (13). Exogenously applied H2S donors protected various lung damages, including acute and chronic lung injury, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and hypoxia-induced pulmonary hypertension (20, 48). H2S was effective in reversing lung inflammation and improving pulmonary function in various animal models of lung injury induced by cigarette smoke, lipopolysaccharide, cerulein, hypoxia, oxygen, burn, resuscitated hemorrhagic shock, and infrarenal aortic cross-clamping (3, 34, 37, 39, 44, 54, 55, 57, 61, 62). Often, CSE blockage by PPG further aggravated the severity of lung injury in some of these models. N-acetyl cysteine (NAC) is a potential H2S-releasing donor and a strong antioxidant (19). The application of NAC to patients with pneumonia reduced oxidative stress and inflammatory response (68). It is proposed that NAC may protect COVID-19-associated cytokine storm and acute respiratory distress syndrome (4, 22). Moreover, prolonged mechanical ventilation often causes lung injury; however, one study observed that intravenous administration of H2S donor increased the tension of oxygen in blood and improved lung function in a rat model of mechanical ventilation injury (57). The inflation of rat donor lungs with H2S during the warm ischemia phase improved mitochondrial functions and attenuated graft ischemic-reperfusion injury after lung transplantation (44). Not only providing protection against lung damage, H2S is also involved in amelioration of the functions of other organs, such as heart and kidney (18, 66). COVID-19 is often manifested as pneumonia with a prominent incidence of cardiovascular complications and also kidney
failure (14, 73). In consideration of these findings, H2S may be a potential remedy for COVID-19 by relieving the damage in lungs and other organs.

**PERSPECTIVE**

According to the research advances on H2S signaling in biology and medicine, it is suggested that H2S may be effective in management of COVID-19, especially in high-risk populations with underlying conditions including cardiovascular diseases, diabetes, and kidney disorders. H2S may fight COVID-19 in multiple ways. First, H2S may block SARS-CoV-2 entry into host cells by interfering with ACE2 and TMPRSS2. Second, H2S can inhibit SARS-CoV-2 replication by attenuating syncytium formation and virus assembly and release. Third, H2S can protect SARS-CoV-2-induced lung damage by suppressing immune response and inflammation development (Fig. 1). It is worth noting here that although our knowledge on H2S signaling in biology and medicine have been advanced in the last decades, there are still some gaps for translating to clinical applications, and many practical limitations need to be further addressed. Developing stable and slow-releasing H2S donors or enzyme-specific activator for boosting H2S production with improved organ specificity has always been a challenge. Identification of the molecular targets of H2S and also the downstream signals are vital for drug development. By knowing the real-time change and enzymatic regulation for H2S production in different types of cells under normal and disease conditions, we can definitely compose new therapeutic strategies for combatting a wide spectrum of diseases. Taking all these into consideration, further preclinical investigations with animals and clinical trials with humans are required to validate H2S signaling as a preventive treatment or therapy for COVID-19.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

G.Y. prepared figure and drafted, edited and revised, and approved final version of manuscript.

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