The biologic effect of hydrogen sulfide and its function in various diseases

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Abstract

Introduction: Hydrogen sulfide (H2S), a colorless, water soluble, flammable gas with a characteristic smell of rotten eggs, has been known as a highly toxic gas for several years. However, much like carbon monoxide (CO) and nitric oxide (NO), the initial negative perception of H2S has developed with the discovery that H2S is generated enzymatically in animals under normal conditions. With the result of this discovery, much more work is needed to elucidate the biologic effects of H2S. In recent years, its cytoprotective properties have been recognized in multiple organs and tissues. In particular, H2S plays important roles in combating oxidative species such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) and protect the body from oxidative stress. Therefore, this review discusses the biologic effect of H2S and how it protects cells in various diseases by acting as an antioxidant that reduces excessive amounts of ROS and RNS.

Ethics and dissemination: Ethical approval and informed consent are not required, as the study will be a literature review and will not involve direct contact with patients or alterations to patient care.

Conclusion: H2S has been found to be cytoprotective in oxidative stress in a wide range of physiologic and pathologic conditions, an increasing number of therapeutic potentials of H2S also have been revealed. However, there is still much debate on the clear mechanism of action of H2S, so that the mechanisms of cell signaling that promote cellular survival and organ protection need to be further investigated to provide better H2S-based therapeutics.

Abbreviations: AMPK = adenosine 5'-monophosphate (AMP)-activated protein kinase, ATG5 = autophagy related 5, Bcl-2 = B-cell lymphoma-2, Bcl-xl = B-cell lymphoma-extra large, CAT = catalase, ONOO− = peroxynitrite, CBS = cystathionine β-synthase, CGL or CSE = cystathionine γ-lyase, CNS = central nervous system, CO = carbon monoxide, CoCl2 = cobalt(II) chloride, COX-2 = cyclooxygenase-2, ER = endoplasmic reticulum, ERK = extracellular-signal-regulated kinase, GPx = glutathione peroxidase, GST = glutathione S-transferase, H2O = water, H2O2 = hydrogen peroxide, H2S = hydrogen sulfide, HO-1 = heme oxygenase-1, IL-8 = interleukin-8, KATP = ATP-sensitive potassium channel, KCa = intermediate calcium-dependent potassium channel, Keap-1 = Kelch-like ECH associating protein 1, LTP = long-term potentiation, M1 = mercaptoptpyruvate sulfurtransferase, mTOR = mammalian target of rapamycin, NalH2S = sodium hydrosulfide, NF-κB = nuclear factor kappa B, NMDA = N-methyl-D-aspartate, NO = nitric oxide, Nrf2 = nuclear-factor-E2-related factor-2, O2− = superoxide, PKCe = protein kinase C epsilon type, ROS = reactive oxygen species, siRNA = small interfering RNA, SOD = superoxide dismutase, SR-A = the class A macrophage scavenger receptor, STAT-3 = signal transducer and activator of transcription 3, TNF-α = tumor necrosis factor α, Trx = thioredoxin, TrxR = thioredoxin reductase.

Keywords: biologic effect, hydrogen sulfide (H2S), oxidative stress

1. Introduction

The 1st toxic gas identified as a signal molecule is nitric oxide (NO), which is produced from arginine by NO synthase.[1] Another toxic gas, carbon monoxide (CO), is produced from biliverdin by hemeoxygenase.[2] Both NO and CO were found as smooth muscle relaxants, and recognized later as neurotransmitters.[3–4] Researchers have suggested that NO liberated from postsynaptic neurons may travel back to presynaptic terminals to cause long-term potentiation (LTP) expression, which is thought to be an important mechanism underlying learning and memory in the central nervous system.[5,6] H2S is the 3rd endogenous gasotransmitter followed by NO and CO.[7] It was initially found to be a neuromodulator[8] and facilitate the induction of hippocampal LTP by enhancing the activity of N-methyl-D-aspartate (NMDA) receptors in neurons and increases the influx of Ca2+ into astrocytes.[9] The biosynthesis of H2S has been attributed to 3 endogenous enzymes: cystathionine β-synthase (CBS), cystathionine γ-lyase (CGL or CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST).[10] The desulfhydration of cysteine is considered as the major source of H2S in mammals. CBS and CSE are 2 pyridoxal-5-phosphate-dependent enzymes. CBS is mainly expressed in various regions of the brain and is crucial to the production of H2S in the central nervous system.[11–13] whereas CSE is primarily observed in the cardiovascular system.[14,15] Recently, 3-MST was reported as the 3rd enzyme for H2S production, which is localized at mitochondria and nerve endings.[16,17]
The H2S functions in the secretion of corticotrophin-releasing hormone from serotonergic neurons\textsuperscript{18,19} and in the relaxation of smooth muscle.\textsuperscript{9,20} In addition, H2S shields neurons and cardiac muscles from oxidative stress\textsuperscript{19,21-23} and helps to maintain insulin secretion.\textsuperscript{24,25} H2S has diverse physiologic functions such as relaxing blood vessels, lowering blood pressure,\textsuperscript{26,27} antiapoptosis,\textsuperscript{28} anti-inflammation,\textsuperscript{29} and antioxidative stress.\textsuperscript{30} Among these functions, the role of H2S in antioxidative stress has been one of the main focuses over years.\textsuperscript{31} Here, we summarize the existing knowledge about the antioxidant effect of H2S, highlighting recent advances in our understanding of the ability of H2S to neutralize reactive oxygen species, and further discuss its function in different diseases.

2. Potential mechanisms of H2S in antioxidative stress

2.1. Direct scavenging of ROS

Oxidative stress involves molecular or cellular damage caused by ROS and RNS, resulting from deficiency of antioxidants and/or antioxidant enzyme systems\textsuperscript{32,33} and disrupting the cellular reduction-oxidation balance. Excessive ROS can result in deoxyribonucleic acid damage, protein misfolding, organelle injury, and neuronal synaptic dysfunction.\textsuperscript{34} Geng et al reported that H2S reduces lipid peroxidation in the heart following isoproterenol-induced myocardial ischemic injury by scavenging hydrogen peroxide (H2O2) and superoxide (O2−).\textsuperscript{35} The major ROS/RNS species produced in cells are O2−, H2O2, and NO.\textsuperscript{136} In the ROS scavenging pathway, superoxide dismutase (SOD) transfers O2− to H2O2, which is converted to O2 and H2O by catalase (CAT). Peroxynitrite (ONOO−), a cytotoxic species, and potent oxidant which can lead to tyrosine nitrination and tyrosine residues in proteins, is formed from rapid interaction of O2− and NO.\textsuperscript{37} H2S has been recognized as a direct scavenger of ONOO−. Tyrosine nitrination and cell toxicity induced by ONOO− can be significantly induced by NaHS pretreatment at 30 μM in human neuroblastoma cell line SH-SY5Y under physiologic condition.\textsuperscript{38} Additionally, it has been reported that H2S can shield mouse brain neuroblastoma Neuro2a cells from oxidative stress mediated by H2O2 and restore glutathione levels suppressed by H2O2.\textsuperscript{39} Similarly, Whiteman and his colleagues have shown that H2S can convert NO to form a novel nitrosothiol compound in vitro, indicating that H2S directly interacts with NO-free radicals to reduce oxidative injury.\textsuperscript{40} Collectively, H2S protects cells in various models of cellular injury by acting as a direct scavenger that reduces excessive amounts of ROS.

2.2. Nrf2-ROS-AMPK signaling pathway

The H2S protects cells from oxidative stress via 2 distinct mechanisms: it either acts as a direct scavenger of ROS or upregulates antioxidant defense system. A research indicated that H2S could upregulate endogenous antioxidants through a nuclear-factor-E2-related factor-2 (Nrf2)-dependent signaling pathway.\textsuperscript{41} Nrf2, a member of the NF-E2 family of nuclear basic leucine zipper transcription factors, regulates gene expression of a wide range of enzymes that serve to attenuate oxidative stress.\textsuperscript{42} In mammals, Nrf2 plays an essential role in oxidative and electrophilic stress responses.\textsuperscript{43} This regulation is mediated by Nrf2 binding to the antioxidant response element or enhancer sequence which is found in the promoter region of certain genes such as heme oxygenase-1 (HO-1), thioredoxin (Trx), glutathione S-transferase (GST), glutathione peroxidase (GPx), thioredoxin reductase (TrXR), and catalase.\textsuperscript{44} In the cytoplasm, Nrf2 couples with Kelch-like ECH-associating protein 1 (Keap-1), which inhibits its transfer into the nucleus. H2S promotes s-sulfhydrate Keap1 releasing Nrf2, which helps Nrf2 translocation into the nucleus.\textsuperscript{45} Calvert et al demonstrated that 30 minutes following the treatment of H2S, Nrf2 assembled in the nucleus in cardiac tissue, and remained at an increased level for at least 2 hours. Moreover, the protein expression of HO-1 and Trx1 was found to be elevated 24 hours following H2S treatment.\textsuperscript{46} Liu et al also reported that H2S decreased high glucose-induced autophagy in endothelial cells through the Nrf2-ROS-AMPK signaling pathway. Administration of 100 μmol/kg NaHS could protect mouse arterial endothelial cells against excessive autophagy induced by type II diabetes and attenuate the impairment of expressions and activities of SOD and CAT.\textsuperscript{47} A role of Nrf2 in regulating the antioxidative stress of H2S is further supported by the finding that garlic oil, a reported H2S donor can induce Nrf2 activation.\textsuperscript{48}

2.3. SR-A signaling pathway

The SR-A, the class A macrophage scavenger receptor, is primarily expressed on the Golgi apparatus or on the plasma membrane of macrophages.\textsuperscript{49} It is essential in several macrophage-associated pathologic conditions resulting from noninfectious diseases, such as adhesion, phagocytosis, and atherosclerosis.\textsuperscript{49-51} SR-A may promote the host innate immune response by regulating direct phagocytosis of pathogenic bacteria and recognizing various pathogen-associated molecular patterns.\textsuperscript{132,133} In addition, SR-A activation could suppress endoplasmic reticulum (ER) stress-induced autophagy in macrophages.\textsuperscript{52} A recent study shows that administration of 100 μg/kg NaHS (ip injection) after 50 minutes of ischemia could attenuate renal ischemia/reperfusion injury by suppressing ER stress-induced autophagy via SR-A signaling pathway in rats.\textsuperscript{53} SR-A is also a potential regulatory factor of oxidative stress and concomitant inflammation.\textsuperscript{54} Kobayashi et al reported that hyperoxia increases SR-A expression in murine lungs, while SR-A deficiency exacerbates oxidative lung injury with increased levels of tumor necrosis factor-α (TNF-α). They also confirmed that intrapulmonary SR-A expression reduces macrophage activation by inhibiting the production of proinflammatory cytokines and protects against oxidative stress.\textsuperscript{55}

2.4. Modulation of GSH

The H2S protects neurons from oxidative stress and improves the viability of cells by increasing the production of intracellular GSH, a major antioxidant in the cellular defense against oxidative stress.\textsuperscript{15,21} H2S redistributes GSH to mitochondria, which generate mainly ROS. As an additional mechanism, H2S produced by 3-MST with CAT in mitochondria might directly reduce oxidative stress and protect cells. Kimura et al demonstrated that H2S reduces cystine to cysteine in the extracellular space and increases cysteine in cell to produce GSH, and that the cysteine transport in the presence of H2S leads to GSH synthesis to a greater extent than does cystine transport. Since H2S does not inhibit the transport of GSH from cytoplasm into mitochondria but efficiently increases mitochondrial GSH, the increase of mitochondrial GSH by H2S may contribute greatly to the
protection of cells from oxidative stress.\[25\] Moreover, upon oxidative stress caused by ischemia/reperfusion, GSH levels are decreased. Total GSH was significantly decreased in mitochondria prepared from severely ischemic focal tissue in both the striatum and cerebral cortex,\[59\] while H2S can recover the GSH levels reduced by ischemia/reperfusion in utero. This observation also supports that H2S increases intracellular GSH concentrations by increasing the transport of cysteine to a greater extent than that of cystine.

Collectively, the potential mechanisms of antioxidation effects of H2S are summarized in Figure 1.

3. The effects of H2S in different tissues

3.1. Role of H2S as antioxidants in central nervous system

In the central nervous system (CNS), H2S participates in diverse physiologic processes, including neurotransmission\[60\] and neuroprotection.\[61\] H2S inhalation has a neuroprotective effect in a mouse model of Parkinson disease.\[62\] H2S could protect neurons from apoptosis and degeneration\[63\] by exerting anti-inflammatory effects, upregulating antioxidant enzyme levels,\[60\] decreasing ROS and the aggregation of lipid peroxidation products. Kimura et al demonstrated that H2S could protect neurons from cell death by increasing the levels of the antioxidant, glutathione using a model of glutamate-induced oxidative stress. They found that H2S increased glutathione levels by enhancing the activity of γ-glutamylcysteine synthetase and upregulating cystine transport.\[19\] Furthermore, H2S restrains the biologic activity of ONOO\(^{-}\) formed in the reaction of NO with superoxide anion.\[64\] Keszler et al reported that H2S may act as an antioxidant by scavenging ROS directly and by reducing glutathione disulfide.\[65\] Increased levels of ROS are detected at inflammation sites. Removal of ROS can be found by supplying homocysteine, and stimulated H2S synthesis expedites the antioxidant activity.\[66\] It should be noticed that high concentrations of H2S cause production of ROS and RNS, whereas lower levels of H2S could react with H2O2, ONOO\(^{-}\), and O2\(^{-}\).\[17,67\] Additionally, H2S performs a cell-signaling function in the CNS by initiating NMDA receptors and increasing intracellular Ca\(^{2+}\) by activating voltage-gated sodium channels in neuronal cells. By doing so, it performs antioxidant functions by upregulating generation of GSH and mitigating oxidative stresses in cells.\[68\]

3.2. H2S and cardioprotection

There is substantial evidence that indicates the production of ROS as an initial cause of injury to the myocardium following ischemia-reperfusion. ROS formed during oxidative stress can stimulate lipid peroxidation, oxidize proteins to inactive states, and cause DNA strand breaks.\[69\] Therefore, the property of cardiac myocytes to remain homeostasis during periods of oxidative stress resides in the ability to activate and induce protective enzymes.\[70\] Geng et al found that H2S reduces lipid peroxidation in the heart following isoproterenol-induced myocardial ischemic injury by scavenging H2O2 and O2\(^{-}\).\[135\] Zhang et al demonstrated that the novel H2S donor 8L mitigates...
oxidative stress-induced injury in H9c2 cardiomyocytes and the mechanisms may be associated with the activation of Nrf2.\textsuperscript{[71]} Meanwhile, the generation of ROS, activation of nuclear factor kappa B (NF-κB), increased expressions of cell adhesion cytokines and induction of apoptosis, which were all regarded as the key promoters of pathology, were all found suppressed by H\textsubscript{2}S.\textsuperscript{[72-75]} This might be the potential mechanisms by which H\textsubscript{2}S could diminish the plaques in arteries and attenuate the atherosclerotic injury, indicating the anti-inflammation effect of H\textsubscript{2}S is benefit for the cardiovascular protection. NaHS caused cardioprotection, in terms of cell viability and electrically induced calcium Ca\textsuperscript{2+} transients.\textsuperscript{[74]} In cultured cardiomyocytes, NaHS was found concentration-dependent inhibitory effects of apoptosis induced by hypoxia/reoxygenation.\textsuperscript{[73]} NaHS also significantly increased cell viability, percentage of rod-shaped cells, and myocyte contractility.\textsuperscript{[76]} More specifically, H\textsubscript{2}S increased the nuclear localization of Nrf2 and the phosphorylation of signal transducer and activator of transcription 3 (STAT-3) and protein kinase C epsilon type (PKCe). Furthermore, H\textsubscript{2}S increased the expression of HO-1 and trx-1, heat shock proteins 90 and 70, B-cell lymphoma-2 (Bcl-2), B-cell lymphoma-extra large (Bcl-xL), and cyclooxygenase-2 (COX-2), and also inactivated the proapoptogen Bad.\textsuperscript{[80]} Administration of H\textsubscript{2}S, either prior to ischemia or at reperfusion, considerably recovers in vitro or in vivo myocardial and ischemia-reperfusion injury.

3.3. H\textsubscript{2}S in diabetes
Diabetes, a serious chronic metabolic disorder, results from the absolute or/and relative deficiency of insulin. The pathogenesis of diabetes is related to decreased functional β-cell mass and increased activities of ATP-sensitive potassium channel (K\textsubscript{ATP}) in pancreatic β cells.\textsuperscript{[77,78]} Jain et al found that H\textsubscript{2}S levels in blood are significantly lower in type 2 diabetes patients than in age-matched healthy subjects. Low blood H\textsubscript{2}S levels may cause the vascular inflammation observed in diabetes because treatment with H\textsubscript{2}S can inhibit inflammatory factor monocyte chemo-attractant protein 1 and interleukin-8 (IL-8) secretion by monocytes cultured in high-glucose medium.\textsuperscript{[79]} Administration with NaHS (50 mol/L) could prevent high-glucose-induced apoptosis in endothelial cells by upregulating SOD activity, reducing ROS generation and malondialdehyde levels, and downregulating the Bax/Bcl-2 ratio.\textsuperscript{[80]} It has been reported that H\textsubscript{2}S could also ameliorate diabetes nephropathy by acting as an ACE inhibitor.\textsuperscript{[81]} These researches suggest that H\textsubscript{2}S has beneficial effects on the control of diabetes owing to its anti-inflammatory and antioxidative functions. Therefore, supplementation with H\textsubscript{2}S could be considered as a potential access to maintain diabetic blood vessel potency.\textsuperscript{[82]}

3.4. Role of H\textsubscript{2}S in skin disorders
The NaH\textsubscript{2}S promoted the viability, induced the differentiation, and enhanced autophagic activity in a dose-dependent manner in HaCaT cells but had no effect on cell apoptosis. Blockage of autophagy by ATG5 siRNA inhibited NaH\textsubscript{2}S-induced cell proliferation and differentiation.\textsuperscript{[83]} This prosurvival effect of H\textsubscript{2}S is in line with the results reported by Yang et al who found that H\textsubscript{2}S help HaCaT cells recover from CoCl\textsubscript{2} and methyl-glyoxal induced injuries and behavior dysfunction through improvement of mitochondrial function and oxidative status, indicating H\textsubscript{2}S may benefit the delayed wound healing in diabetes.\textsuperscript{[84,85]}

Proliferation and differentiation of keratinocytes are indispensable process of wound repair and are dysregulated under pathologic conditions such as psoriasis, epidermal cancers, and atopic dermatitis.\textsuperscript{[86,87]} Thus, the identification of H\textsubscript{2}S as a stimulus for keratinocyte proliferation and differentiation provides essential information for understanding epidermal repair and disease, and also offers potential targets for therapy. Recent studies have demonstrated that H\textsubscript{2}S can accelerate diabetic wound healing by promoting angiogenesis and restoring endothelial progenitor cell function.\textsuperscript{[88]} In addition, H\textsubscript{2}S could restore a normal morphologic phenotype in Werner syndrome fibroblasts, attenuates oxidative damage, and modulates mTOR pathway.\textsuperscript{[89]}

Psoriasis is a common T-cell-chronic inflammatory skin disease characterized by circumscribed, red, thickened plaques with an overlying silver-white scale. Ammar KH Alshorafa found that psoriatic patients exhibited lower serum levels of H\textsubscript{2}S compared to healthy individuals, suggesting that H\textsubscript{2}S may play a protective role in the pathogenesis of psoriasis. Exogenous H\textsubscript{2}S inhibited the TNF-α-mediated upregulation of NO, IL-6, and IL-8 in a dose-dependent manner. In addition, H\textsubscript{2}S inhibited TNF-α-mediated activation of p38, extracellular-signal-regulated kinase (ERK), and NF-κB, making H\textsubscript{2}S-releasing agents promising therapeutics for psoriasis.\textsuperscript{[90]} It was also suggested that supplementation with H\textsubscript{2}S may represent an alternative for psoriasis, because it greatly reduced signs and symptoms of a psoriasis-like skin model.\textsuperscript{[91]}

Additionally, a sulfur-rich balneotherapy has been suggested to be an effective treatment of psoriasis.\textsuperscript{[92]} Therefore, it would be particularly interesting to explore whether H\textsubscript{2}S plays a therapeutic role by mediating keratinocyte proliferation and differentiation in psoriasis in vivo.

Other researches also demonstrated that H\textsubscript{2}S donors confer protective effect against histamine-induced acute pruritus and cutaneous inflammation. These effects can be mediated by stabilizing mast cells, known to contain various mediators, and to be primary initiators of allergic processes, thus making of H\textsubscript{2}S donors a potential alternative/complementary therapy for treating inflammatory allergic skin diseases and related pruritus.\textsuperscript{[93]} Exogenous H\textsubscript{2}S elicits cutaneous vasodilatation mediated by intermediate calcium-dependent potassium channel (K\textsubscript{Ca}) and has a functional interaction with both NO and COX vaso-dilatory signaling pathways.\textsuperscript{[94]} Further advancement of pH\textsubscript{4}, oxygen and free radical-sensitive donors will be helpful to achieve selective delivery of H\textsubscript{2}S.

4. Conclusion
Experiments performed in recent years have shed light on the biologic and pharmacologic roles of H\textsubscript{2}S in a wide range of physiologic and pathologic conditions, an increasing number of therapeutic potentials of H\textsubscript{2}S also have been revealed. This gas has been found to be cytoprotective in oxidative stress in many organ systems. H\textsubscript{2}S-donating drugs have been synthesized and tested in vivo and in vitro.\textsuperscript{[95]} Chattopadhyay et al showed that H\textsubscript{2}S releasing nonsteroidal anti-inflammatory drugs (HS-NSAIDs) inhibited proliferation, induced apoptosis, and caused G0/G1 cell cycle block of HT-29 colon cancer cells.\textsuperscript{[96]} John et al established that HS-NSAIDs inhibited cyclooxygenase-1 and cyclooxygenase-2 activity as effectively as NSAIDs, and reduced the prostaglandin synthesis. In addition, HS-NSAIDs did not induce leukocyte adherence while NSAIDs did.\textsuperscript{[97]} Agents which specifically stimulate various H\textsubscript{2}S-producing enzymes (CSE, CBS, and 3MST) are promising therapeutic candidates to study.
However, there is still much debate on the clear mechanism of action of H₂S, so that the mechanisms of cell signaling that promote cellular survival and organ protection need to be further investigated across a wide array of disease states in a number of animal species. It is also of extreme importance to reach an understanding of the mechanism of H₂S release, modulation of animal species. It is also of extreme importance to reach an investigated across a wide array of disease states in a number of promote cellular survival and organ protection need to be further.

Author contributions

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