Systematic Review and Meta-Analysis

Medicine®

OPEN

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

Qing Xiao, MD, Jiayi Ying, MD, Leihong Xiang, MD, PhD, Chengfeng Zhang, MD, PhD*

Abstract

Introduction: Hydrogen sulfide (H_2S), 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 H_2S has developed with the discovery that H_2S 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 H_2S. In recent years, its cytoprotective properties have been recognized in multiple organs and tissues. In particular, H_2S 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 H_2S 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: H_2S 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 H_2S also have been revealed. However, there is still much debate on the clear mechanism of action of H_2S, so that the mechanisms of cell signaling that promote cellular survival and organ protection need to be further investigated to provide better H_2S-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, $CoCl_2$ = cobalt(II) chloride, COX-2 = cyclooxygenase-2, ER = endoplasmic reticulum, ERK = extracellular-signal-regulated kinase, GPx = glutathione peroxidase, GST = glutathione *S*-transferase, H_2O = water, H_2O_2 = hydrogen peroxide, H_2S = hydrogen sulfide, HO-1 = heme oxygenase-1, IL-8 = interleukin-8, K_{ATP} = ATP-sensitive potassium channel, K_{Ca} = intermediate calcium-dependent potassium channel, Keap-1 = Kelch-like ECH associating protein 1, LTP =long-term potentiation, 3-MST = 3-mercaptopyruvate sulfurtransferase, mTOR = mammalian target of rapamycin, NaHS = sodium hydrosulfide, NF-κB = nuclear factor kappa B, NMDA = *N*-methyl-D-aspartate, NO = nitric oxide, Nrf2 = nuclear-factor-E2-related factor-2, O_2 = oxygen, O_2^- = superoxide, PKCε = protein kinase C epsilon type, RNS = reactive nitrogen species, 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 = thrioredoxin reductase.

Keywords: biologic effect, hydrogen sulfide (H_2S), 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] H_2S 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 Ca^{2+} into astrocytes.[9] The biosynthesis of H_2S 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 H_2S 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 H_2S 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 H_2S production, which is localized at mitochondria and nerve endings.[16,17]

Editor: Abdelouahab Bellou.

This work was supported by Grants from the Natural Science Foundation of China (No. 81573064, 81502748, and 81472901).

The authors have no conflicts of interest to disclose.

Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China.

** Correspondence: Chengfeng Zhang, Huashan Hospital Fudan University, Shanghai, Shanghai, China (e-mail: e3dangdang@hotmail.com).*

Medicine (2018) 97:44(e13065)

Received: 14 August 2018 / Accepted: 8 October 2018

http://dx.doi.org/10.1097/MD.0000000000013065

The H_2S functions in the secretion of corticotrophin-releasing hormone from serotonergic neurons[18,19] and in the relaxation of smooth muscle.[9,20] In addition, H_2S shields neurons and cardiac muscles from oxidative stresses[19,21–23] and helps to maintain insulin secretion.[24,25] H_2S has diverse physiologic functions such as relaxing blood vessels, lowering blood pressure,[26,27] antiapoptosis,[28] anti-inflammation,[29] and anti-oxidative stress.[30] Among these functions, the role of H_2S in antioxidative stress has been one of the main focuses over years.[31] Here, we summarize the existing knowledge about the antioxidant effect of H_2S, highlighting recent advances in our understanding of the ability of H_2S to neutralize reactive oxygen species, and further discuss its function in different diseases.

2. Potential mechanisms of H_2S 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[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.[34] Geng et al reported that H_2S reduces lipid peroxidation in the heart following isoproterenol-induced myocardial ischemic injury by scavenging hydrogen peroxide (H_2O_2) and superoxide (O_2^-).[35] The major ROS/RNS species produced in cells are O_2^-, H_2O_2, and NO.[36] In the ROS scavenging pathway, superoxide dismutase (SOD) transfers O_2^- to H_2O_2, which is converted to O_2 and H_2O by catalase (CAT). Peroxynitrite ($ONOO^-$), a cytotoxic species, and potent oxidant which can lead to tyrosine nitration and tyrosine residues in proteins, is formed from rapid interaction of O_2^- and NO.[37] H_2S has been recognized as a direct scavenger of $ONOO^-$. Tyrosine nitration and cell toxicity induced by $ONOO^-$ can be significantly inhibited by NaHS pretreatment at 30 μM in human neuroblastoma cell line SH-SY5Y under physiologic condition.[38] Additionally, it has been reported that H_2S can shield mouse brain neuroblastoma Neuro2a cells from oxidative stress mediated by H_2O_2 and restore glutathione levels suppressed by H_2O_2.[25] Similarly, Whiteman and his colleagues have shown that H_2S can convert NO to form a novel nitrosothiol compound in vitro, indicating that H_2S directly interacts with NO-free radicals to reduce oxidative stress.[39] Collectively, H_2S 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 H_2S 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 H_2S could upregulate endogenous antioxidants through a nuclear-factor-E2-related factor-2 (Nrf2)-dependent signaling pathway.[40] 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.[41] In mammals, Nrf2 plays an essential role in oxidative and electrophilic stress responses.[42] This regulation is mediated by Nrf2 binding to the antioxidant responsive element, a cis-acting regulatory 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), thrioredoxin reductase (TrxR), and catalase.[43,44] In the cytoplasm, Nrf2 couples with Kelch-like ECH-associating protein 1 (Keap-1), which inhibits its transfer into the nucleus. H_2S promotes *s*-sulfhydrate Keap1 releasing Nrf2, which helps Nrf2 translocation into the nucleus.[28] Calvert et al demonstrated that 30 minutes following the treatment of H_2S, 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 H_2S treatment.[45] Liu et al also reported that H_2S 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.[46] A role of Nrf2 in regulating the antioxidative stress of H_2S is further supported by the finding that garlic oil, a reported H_2S donor can induce Nrf2 activation.[47]

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.[48] It is essential in several macrophage-associated pathologic conditions resulting from noninfectious diseases, such as adhesion, phagocytosis, and atherosclerosis.[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.[52,53] In addition, SR-A activation could suppress endoplasmic reticulum (ER) stress-induced autophagy in macrophages.[54] 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.[55] SR-A is also a potential regulatory factor of oxidative stress and concomitant inflammation.[56,57] 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.[58]

2.4. Modulation of GSH

The H_2S 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.[19,21] H_2S redistributes GSH to mitochondria, which generate mainly ROS. As an additional mechanism, H_2S produced by 3-MST with CAT in mitochondria might directly reduce oxidative stress and protect cells. Kimura et al demonstrated that H_2S 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 H_2S leads to GSH synthesis to a greater extent than does cystine transport. Since H_2S does not inhibit the transport of GSH from cytoplasm into mitochondria but efficiently increases mitochondrial GSH, the increase of mitochondrial GSH by H_2S may contribute greatly to the

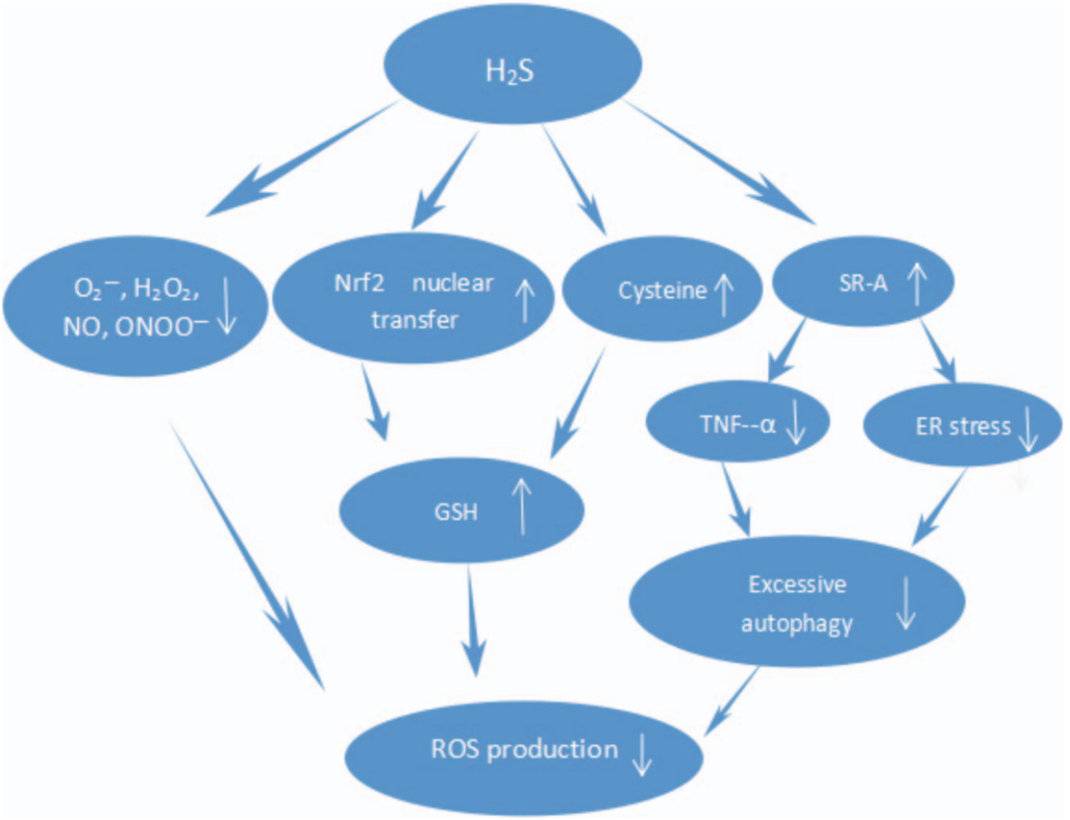

Figure 1. Potential mechanisms of antioxidation effects H_2S. ER = endoplasmic reticulum, GSH = glutathione, H_2S = hydrogen sulfide, Nrf2 = NF-E2-related factor 2, ROS = reactive oxygen species, SR-A = scavenger receptor class A, TNF-α = tumor necrosis factor α.

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 H_2S can recover the GSH levels reduced by ischemia/reperfusion in utero. This observation also supports that H_2S 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 H_2S are summarized in Figure 1.

3. The effects of H_2S in different tissues

3.1. Role of H_2S as antioxidants in central nervous system

In the central nervous system (CNS), H_2S participates in diverse physiologic processes, including neurotransmission[60] and neuroprotection.[61] H_2S inhalation has a neuroprotective effect in a mouse model of Parkinson disease.[62] H_2S could protect neurons from apoptosis and degeneration[63] by exerting anti-inflammatory effects, upregulating antioxidant enzyme level,[60] decreasing ROS and the aggregation of lipid peroxidation products. Kimura et al demonstrated that H_2S 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 H_2S increased glutathione levels by enhancing the activity of γ-glutamylcysteine synthetase and upregulating cystine transport.[19] Furthermore, H_2S restrains the biologic activity of $ONOO^-$ formed in the reaction of NO with superoxide anion.[64] Keszler et al reported that H_2S 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 H_2S synthesis expedites the antioxidant activity.[66] It should be noticed that high concentrations of H_2S cause production of ROS and RNS, whereas lower levels of H_2S could react with H_2O_2, $ONOO^-$, and O_2^-.[17,67] Additionally, H_2S 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. H_2S 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 H_2S reduces lipid peroxidation in the heart following isoproterenol-induced myocardial ischemic injury by scavenging H_2O_2 and O_2^-.[35] Zhang et al demonstrated that the novel H_2S donor 8L mitigates

oxidative stress-induced injury in H9c2 cardiomyocytes and the mechanisms may be associated with the activation of Nrf2.[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_2S.[72,73] This might be the potential mechanisms by which H_2S could diminish the plaques in arteries and attenuate the atherosclerotic injury, indicating the anti-inflammation effect of H_2S is benefit for the cardiovascular protection. NaHS caused cardioprotection, in terms of cell viability and electrically induced calcium Ca^{2+} transients.[74] In cultured cardiomyocytes, NaHS was found concentration-dependent inhibitory effects of apoptosis induced by hypoxia/reoxygenation.[75] NaHS also significantly increased cell viability, percentage of rod-shaped cells, and myocyte contractility.[76] More specifically, H_2S 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 (PKCε). Furthermore, H_2S 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.[40] Administration of H_2S, either prior to ischemia or at reperfusion, considerably recovers in vitro or in vivo myocardial and ischemia-reperfusion injury.

3.3. H_2S 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_{ATP}) in pancreatic β cells.[77,78] Jain et al found that H_2S levels in blood are significantly lower in type 2 diabetes patients than in age-matched healthy subjects. Low blood H_2S levels may cause the vascular inflammation observed in diabetes because treatment with H_2S can inhibit inflammatory factor monocyte chemoattractant protein 1 and interleukin-8 (IL-8) secretion by monocytes cultured in high-glucose medium.[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.[80] It has been reported that H_2S could also ameliorate diabetes nephropathy by acting as an ACE inhibitor.[81] These researches suggest that H_2S may have beneficial effects on the control of diabetes owing to its anti-inflammatory and antioxidative functions. Therefore, supplementation with H_2S could be considered as a potential access to maintain diabetic blood vessel potency.[82]

3.4. Role of H_2S in skin disorders

The NaHS 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 NaHS-induced cell proliferation and differentiation.[83] This prosurvival effect of H_2S is in line with the results reported by Yang et al who found that H_2S help HaCaT cells recover from $CoCl_2$ and methylglyoxal induced injuries and behavior dysfunction through improvement of mitochondrial function and oxidative status, indicating H_2S may benefit the delayed wound healing in diabetes.[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.[86,87] Thus, the identification of H_2S 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_2S can accelerate diabetic wound healing by promoting angiogenesis and restoring endothelial progenitor cell function.[88] In addition, H_2S could restore a normal morphologic phenotype in Werner syndrome fibroblasts, attenuates oxidative damage, and modulates mTOR pathway.[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_2S compared to healthy individuals, suggesting that H_2S may play a protective role in the pathogenesis of psoriasis. Exogenous H_2S inhibited the TNF-α-mediated upregulation of NO, IL-6, and IL-8 in a dose-dependent manner. In addition, H_2S inhibited TNF-α-mediated activation of p38, extracellular-signal-regulated kinase (ERK), and NF-κB, making H_2S-releasing agents promising therapeutics for psoriasis.[90] It was also suggested that supplementation with H_2S may represent an alternative for psoriasis, because it greatly reduced signs and symptoms of a psoriasis-like skin model.[91] Additionally, a sulfur-rich balneotherapy has been suggested to be an effective treatment of psoriasis.[92] Therefore, it would be particularly interesting to explore whether H_2S plays a therapeutic role by mediating keratinocyte proliferation and differentiation in psoriasis in vivo.

Other researches also demonstrated that H_2S 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_2S donors a potential alternative/complementary therapy for treating inflammatory allergic skin diseases and related pruritus.[93] Exogenous H_2S elicits cutaneous vasodilatation mediated by intermediate calcium-dependent potassium channel (K_{Ca}) and has a functional interaction with both NO and COX vasodilatatory signaling pathways.[94] Further advancement of pH, oxygen and free radical-sensitive donors will be helpful to achieve selective delivery of H_2S.

4. Conclusion

Experiments performed in recent years have shed light on the biologic and pharmacologic roles of H_2S in a wide range of physiologic and pathologic conditions, an increasing number of therapeutic potentials of H_2S also have been revealed. This gas has been found to be cytoprotective in oxidative stress in many organ systems. H_2S-donating drugs have been synthesized and tested in vivo and in vitro.[95] Chattopadhyay et al showed that H_2S releasing nonsteroidal anti-inflammatory drugs (HS-NSAIDs) inhibited proliferation, induced apoptosis, and caused G0/G1 cell cycle block of HT-29 colon cancer cells.[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.[97] Agents which specifically stimulate various H_2S-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 H_2S, 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 H_2S release, modulation of synthesis and broken down, to provide an avenue for future benefits of how H_2S can be used as clinical therapeutic applications.

Author contributions

Conceptualization: Qing Xiao, Leihong Xiang, Chengfeng Zhang.
Writing – original draft: Qing Xiao, Jiayi Ying.
Writing – review & editing: Chengfeng Zhang.
Chengfeng Zhang orcid: 0000-0002-1302-5667.

References

[1] Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373–6.
[2] Verma A, Hirsch DJ, Glatt CE, et al. Carbon monoxide: a putative neural messenger. Science 1993;259:381–4.
[3] O'Dell TJ, Hawkins RD, Kandel ER, et al. Tests of the roles of two diffusible substances in long-term potentiation: evidence for nitric oxide as a possible early retrograde messenger. Proc Natl Acad Sci U S A 1991;88:11285–9.
[4] Stevens CF, Wang Y. Reversal of long-term potentiation by inhibitors of haem oxygenase. Nature 1993;364:147–9.
[5] Schuman EM, Madison DV. A requirement for the intercellular messenger nitric oxide in long-term potentiation. Science 1991;254: 1503–6.
[6] Huang , Emily P. Synaptic plasticity: a role for nitric oxide in LTP. Curr Biol 1997;7:141–3.
[7] Chen J, Gao J, Sun W, et al. Involvement of exogenous H_2S in recovery of cardioprotection from ischemic post-conditioning via increase of autophagy in the aged hearts. Int J Cardiol 2016;220:681–92.
[8] Abe K, Kimura H. The possible role of hydrogen sulfide as an endogenous neuromodulator. J Neurosci 1996;16:1066–71.
[9] Hosoki R, Matsuki N, Kimura H. The possible role of hydrogen sulfide as an endogenous smooth muscle relaxant in synergy with nitric oxide. Biochem Biophys Res Commun 1997;237:527–31.
[10] Szczesny B, Marcatti M, Zatarain JR, et al. Inhibition of hydrogen sulfide biosynthesis sensitizes lung adenocarcinoma to chemotherapeutic drugs by inhibiting mitochondrial DNA repair and suppressing cellular bioenergetics. Sci Rep 2016;6:36125.
[11] Kotsyuba EP. Cystathionine β-synthase in the central nervous system of the shore crab Hemigrapsus sanguineus. *Doklady Biol Sci 2011;437:94–6*.
[12] Chertok VM, Kotsiuba AE, Kotsiuba EP. Cystathionine beta-synthase in the structural elements of the human brain and spinal cord [in Russian]. Tsitologiia 2011;53:665–70.
[13] Robert K, Vialard F, Thiery E, et al. Expression of the cystathionine synthase (CBS) gene during mouse development and immunolocalization in adult brain. J Histochem Cytochem 2003;51:363–71.
[14] Geng B, Yang J, Qi Y, et al. H2S generated by heart in rat and its effects on cardiac function. Biochem Biophys Res Commun 2004;313:362–8.
[15] Mishra PK, Tyagi N, Sen U, et al. H2S ameliorates oxidative and proteolytic stresses and protects the heart against adverse remodeling in chronic heart failure. Am J Physiol Heart Circ Physiol 2010;298:H451–6.
[16] Shibuya N, Tanaka M, Yoshida M, et al. 3-Mercaptopyruvate sulfurtransferase produces hydrogen sulfide and bound sulfane sulfur in the brain. Antioxid Redox Signal 2009;11:703–14.
[17] Mikami Y, Shibuya N, Kimura Y, et al. Thioredoxin and dihydrolipoic acid are required for 3-mercaptopyruvate sulfurtransferase to produce hydrogen sulfide. Biochem J 2011;439:479–85.
[18] Van Laar VS, Arnold B, Cassady SJ, et al. Bioenergetics of neurons inhibit the translocation response of Parkin following rapid mitochondrial depolarization. Hum Mol Genet 2011;20:927–40.
[19] Kimura Y, Kimura H. Hydrogen sulfide protects neurons from oxidative stress. Neurosci Res 2011;71:e88–188.
[20] Zhao W, Zhang J, Lu Y, et al. The vasorelaxant effect of H2S as a novel endogenous gaseous KATP channel opener. EMBO J 2014;20:6008–16.
[21] Kimura Y, Dargusch R, Schubert D, et al. Hydrogen sulfide protects HT22 neuronal cells from oxidative stress. Antioxid Redox Signal 2006;8:661–70.
[22] Sivarajah A, Mcdonald MC, Thiemermann C. The production of hydrogen sulfide limits myocardial ischemia and reperfusion injury and contributes to the cardioprotective effects of preconditioning with endotoxin, but not ischemia in the rat. Shock 2006;26:154–61.
[23] Umemura K, Kimura H. Hydrogen sulfide enhances reducing activity in neurons: neurotrophic role of H2S in the brain? Antioxid Redox Signal 2007;9:2035–41.
[24] Kaneko Y, Kimura Y, Kimura H, et al. L-cysteine inhibits insulin release from the pancreatic beta-cell: possible involvement of metabolic production of hydrogen sulfide, a novel gasotransmitter. Diabetes 2006;55:1391–7.
[25] Yang W, Yang G, Jia X, et al. Activation of KATP channels by H2S in rat insulin-secreting cells and the underlying mechanisms. J Physiol 2010;569:519–31.
[26] Yang G, Wu L, Jiang B, et al. H2S as a physiologic vasorelaxant: hypertension in mice with deletion of cystathionine gamma-lyase. Science 2008;322:587–90.
[27] Sun Y, Huang Y, Zhang R, et al. Hydrogen sulfide upregulates K ATP, channel expression in vascular smooth muscle cells of spontaneously hypertensive rats. J Mol Med 2015;93:439–55.
[28] Guo C, Liang F, Shah MW, et al. Hydrogen sulfide protected gastric epithelial cell from ischemia/reperfusion injury by Keap1 s-sulfhydration, MAPK dependent anti-apoptosis and NF-(B dependent anti-inflammation pathway. Eur J Pharmacol 2014;725:70–8.
[29] Du J, Huang Y, Yan H, et al. Hydrogen sulfide suppresses ox-LDL-stimulated monocyte chemoattractant protein-1 generation from macrophages via NF-B pathway. J Biol Chem 2014;289:9741–53.
[30] Zheng J, Zhao T, Yuan Y, et al. Hydrogen sulfide (H_2S) attenuates uranium-induced acute nephrotoxicity through oxidative stress and inflammatory response via Nrf2-NF-B pathways. Chem Biol Interact 2015;242:353–62.
[31] Panthi S, Chung HJ, Jung J, et al. Physiological importance of hydrogen sulfide: emerging potent neuroprotector and neuromodulator. Oxid Med Cell Longev 2016;2016:9049782.
[32] Kneeshaw S, Keyani R, Delorme-Hinoux V, et al. Nucleoredoxin guards against oxidative stress by protecting antioxidant enzymes. Proc Natl Acad Sci U S A 2017;2017:pii: 201703344.
[33] Lv H, Liu Q, Wen Z, et al. Xanthohumol ameliorates lipopolysaccharide (LPS)-induced acute lung injury via induction of AMPK/GSK3β-Nrf2 signal axis. Redox Biol 2017;12:311–24.
[34] Maiese K. New insights for oxidative stress and diabetes mellitus. Oxid Med Cell Longev 2015;2015:875961.
[35] Geng B, Chang L, Pan C, et al. Endogenous hydrogen sulfide regulation of myocardial injury induced by isoproterenol. Biochem Biophys Res Commun 2014;318:756–63.
[36] Fransen M, Nordgren M, Wang B, et al. Role of peroxisomes in ROS/RNS-metabolism: implications for human disease. Biochim Biophys Acta 2012;1822:1363–73.
[37] Van der Vliet A, Eiserich JP, O'Neill CA, et al. Tyrosine modification by reactive nitrogen species: a closer look. Arch Biochem Biophy 1995; 319:341–9.
[38] Whiteman M, Armstrong JS, Chu SH, et al. The novel neuromodulator hydrogen sulfide: an endogenous peroxynitrite 'scavenger'? J Neurochem 2010;90:765–8.
[39] Kimura Y, Goto Y, Kimura H. Hydrogen sulfide increases glutathione production and suppresses oxidative stress in mitochondria. Antioxid Redox Signal 2010;12:1–3.
[40] Calvert JW, Jha S, Gundewar S, et al. Hydrogen sulfide mediates cardioprotection through Nrf2 signaling. Circ Res 2009;105:365–74.
[41] Fisher CD, Augustine LM, Maher JM, et al. Induction of drug-metabolizing enzymes by garlic and allyl sulfide compounds via activation of constitutive androstane receptor and nuclear factor E2-related factor 2. Drug Metab Dispos 2007;35:995–1000.
[42] Suzuki T, Seki S, Hiramoto K, et al. Hyperactivation of Nrf2 in early tubular development induces nephrogenic diabetes insipidus. Nat Commun 2017;8:14577.
[43] Tanito M, Agbaga MP, Anderson RE. Upregulation of thioredoxin system via Nrf2-antioxidant responsive element pathway in adaptive-retinal neuroprotection in vivo and in vitro. Free Radic Biol Med 2007;42:1838–2185.
[44] Zhu H, Itoh K, Yamamoto M, et al. Role of Nrf2 signaling in regulation of antioxidants and phase 2 enzymes in cardiac fibroblasts: protection

against reactive oxygen and nitrogen species-induced cell injury. FEBS Lett 2005;579:3029–36.
[45] Benavides GA, Squadrito GL, Mills RW, et al. Hydrogen sulfide mediates the vasoactivity of garlic. Proc Natl Acad Sci U S A 2007;104:17977–82.
[46] Liu J, Wu J, Sun A, et al. Hydrogen sulfide decreases high glucose/palmitate-induced autophagy in endothelial cells by the Nrf2-ROS-AMPK signaling pathway. Cell Biosci 2016;6:33.
[47] Joo MS, Kim WD, Lee KY, et al. AMPK facilitates nuclear accumulation of Nrf2 by phosphorylating at serine 550. Mol Cell Biol 2016;36:1931–42.
[48] Xu Z, Xu L, Li W, et al. Innate scavenger receptor-A regulates adaptive T helper cell responses to pathogen infection. Nat Commun 2017;8:16035.
[49] PrabhuDas MR, Baldwin CL, Bollyky PL, et al. A consensus definitive classification of scavenger receptors and their roles in health and disease. J Immunol 2017;198:3775–89.
[50] Bai H, Li N, Zhou X, et al. GRP78 inhibits macrophage adhesion via SR-A. J Biomed Res 2014;28:269–74.
[51] Jalkanen J, Leppanen P, Narvanen O, et al. Adenovirus-mediated gene transfer of a secreted decoy human macrophage scavenger receptor (SR-AI) in LDL receptor knock-out mice. Atherosclerosis 2003;169:95–103.
[52] Ganesan S, Faris AN, Comstock AT, et al. Elastase/LPS-exposed mice exhibit impaired innate immune responses to bacterial challenge: role of scavenger receptor A. Am J Pathol 2012;180:61–72.
[53] Canton J, Neculai D, Grinstein S. Scavenger receptors in homeostasis and immunity. Nat Rev Immunol 2013;13:621–34.
[54] Huang H, Li X, Zhuang Y, et al. Class A scavenger receptor activation inhibits endoplasmic reticulum stress-induced autophagy in macrophage. J Biomed Res 2014;28:213–21.
[55] Ling Q, Yu X, Wang T, et al. Roles of the exogenous H2S-mediated SR-A signaling pathway in renal ischemia/reperfusion injury in regulating endoplasmic reticulum stress-induced autophagy in a rat model. Cell Physiol Biochem Int J Exp 2017;41:2461–74.
[56] Ozeki Y, Tsutsui H, Kawada N, et al. Macrophage scavenger receptor down-regulates mycobacterial cord factor-induced proinflammatory cytokine production by alveolar and hepatic macrophages. Microb Pathog 2006;40:171–6.
[57] Beamer CA, Holian A. Scavenger receptor class A type I/II (CD204) null mice fail to develop fibrosis following silica exposure. Am J Physiol Lung Cell Mol Physiol 2005;289:186–95.
[58] Kobayashi H, Sakashita N, Okuma T, et al. Class A scavenger receptor (CD204) attenuates hyperoxia-induced lung injury by reducing oxidative stress. J Pathol 2007;212:38–46.
[59] Anderson MF, Sims NR. The effects of focal ischemia and reperfusion on the glutathione content of mitochondria from rat brain subregions. J Neurochem 2002;81:541–9.
[60] Deng J, Lei C, Chen Y, et al. Neuroprotective gases - fantasy or reality for clinical use? Prog Neurobiol 2014;115:210–45.
[61] Lee SW, Hu YS, Hu LF, et al. Hydrogen sulphide regulates calcium homeostasis in microglial cells. Glia 2006;54:116–24.
[62] Kida K, Yamada M, Tokuda K, et al. Inhaled hydrogen sulfide prevents neurodegeneration and movement disorder in a mouse model of Parkinson's disease. Antioxid Redox Signal 2011;15:343–52.
[63] Olas B. Hydrogen sulfide in signaling pathways. Clin Chim Acta 2015;439:212–8.
[64] Olas B, Wachowicz B. Role of reactive nitrogen species in blood platelet functions. Platelets 2007;18:555–65.
[65] Keszler A, Zhang Y, Hogg N. Reaction between nitric oxide, glutathione, and oxygen in the presence and absence of protein: How are S-nitrosothiols formed? Free Radic Biol Med 2010;48:55–64.
[66] Bruinenberg PG, Roo GD, Limsowtin G. Purification and characterization of cystathionine g-lyase from *Lactococcus lactis* subsp. *cremoris* SK11: possible role in flavor compound formation during cheese maturation. Appl Environ Microbiol 1997;63:561–6.
[67] Kimura H. Hydrogen Sulfide-Mediated Cellular Signaling and Cytoprotection. Hydrogen Sulfide and its Therapeutic Applications. 2013; Springer, Vienna:181–202.
[68] Panthi S, et al. Physiological importance of hydrogen sulfide: emerging potent neuroprotector and neuromodulator. Oxid Med Cell Longev 2016;3:1–1.
[69] Venardos KM, Perkins A, Headrick J, et al. Myocardial ischemia-reperfusion injury, antioxidant enzyme systems, and selenium: a review. Curr Med Chem 2007;14:1539–49.
[70] Kang KW, Lee SJ, Kim SG. Molecular mechanism of nrf2 activation by oxidative stress. Antioxid Redox Signal 2005;7:1664–73.
[71] Zhang P, Zhang H, Yang CT, et al. A novel H2S donor 8L protects H9c2 cardiomyocytes against H_2O_2-induced damage in an NF-E2-related factor 2-dependent manner. Chin J Arterioscler Dis 2015.
[72] Wang Y, Zhao X, Jin H, et al. Role of hydrogen sulfide in the development of atherosclerotic lesions in apolipoprotein E knockout mice. Arterioscler Thromb Vasc Biol 2009;29:173–9.
[73] Pan LL, Liu XH, Gong QH, et al. Hydrogen sulfide attenuated tumor necrosis factor-induced inflammatory signaling and dysfunction in vascular endothelial cells. PLoS One 2011;6:e19766.
[74] Pan TT, Feng ZN, Lee SW, et al. Endogenous hydrogen sulfide contributes to the cardioprotection by metabolic inhibition preconditioning in the rat ventricular myocytes. J Mol Cell Cardiol 2006;40:119–30.
[75] Yao LL, Huang XW, Wang YG, et al. Hydrogen sulfide protects cardiomyocytes from hypoxia/reoxygenation-induced apoptosis by preventing GSK-3beta-dependent opening of mPTP. Am J Physiol Heart Circ Physiol 2010;298:H1310–9.
[76] Hu LF, Pan TT, Neo KL, et al. Cyclooxygenase-2 mediates the delayed cardioprotection induced by hydrogen sulfide preconditioning in isolated rat cardiomyocytes. Pflügers Arch 2008;455:971–8.
[77] Koster JC, Permutt MA, Nichols CG. Diabetes and insulin secretion: the ATP-sensitive K+ channel (K ATP) connection. Diabetes 2005;54:3065–72.
[78] Mathis D, Vence L, Benoist C. beta-Cell death during progression to diabetes. Nature 2001;414:792–8.
[79] Jain SK, Bull R, Rains JL, et al. Low levels of hydrogen sulfide in the blood of diabetes patients and streptozotocin-treated rats causes vascular inflammation? Antioxid Redox Signal 2010;12:1333–7.
[80] Guan Q, Zhang Y, Yu C, et al. Hydrogen sulfide protects against high-glucose-induced apoptosis in endothelial cells. Cardiovasc. Pharmacol 2012;59:188–93.
[81] Suzuki K, Olah G, Modis K, et al. Hydrogen sulfide replacement therapy protects the vascular endothelium in hyperglycemia by preserving mitochondrial function. Proc Natl Acad Sci U S A 2011;108:13829–34.
[82] Szabo C. Roles of hydrogen sulfide in the pathogenesis of diabetes mellitus and its complications. Antioxid Redox Signal 2012;17:68–80.
[83] Xie X, Dai H, Zhuang B, et al. Exogenous hydrogen sulfide promotes cell proliferation and differentiation by modulating autophagy in human keratinocytes. Biochem Biophys Res Commun 2016;472:437–43.
[84] Yang C, Yang Z, Zhang M, et al. Hydrogen sulfide protects against chemical hypoxia-induced cytotoxicity and inflammation in HaCaT cells through inhibition of ROS/NF-(B/COX-2 pathway. PLoS One 2011;6: e21971.
[85] Yang CT, Zhao Y, Xian M, et al. A novel controllable hydrogen sulfide-releasing molecule protects human skin keratinocytes against methylglyoxal-induced injury and dysfunction. Cell Physiol Biochem 2014;34:1304–17.
[86] Angel P, Szabowski A. Function of AP-1 target genes in mesenchyma-lepithelial cross-talk in skin. Biochem Pharmacol 2002;64:949–56.
[87] Oyoshi MK, He R, Kumar L, et al. Cellular and molecular mechanisms in atopic dermatitis. Adv Immunol 2009;102:135–226.
[88] Liu F, Chen DD, Sun X, et al. Hydrogen sulfide improves wound healing via restoration of endothelial progenitor cell functions and activation of angiopoietin-1 in type 2 diabetes. Diabetes 2014;63:1763–78.
[89] Talaei F, van Praag VM, Henning RH. Hydrogen sulfide restores a normal morphological phenotype in Werner syndrome fibroblasts, attenuates oxidative damage and modulates mTOR pathway. Pharmacol Res 2013;74:34–44.
[90] Alshorafa AK, Guo Q, Zeng F, et al. Psoriasis is associated with low serum levels of hydrogen sulfide, a potential anti-inflammatory molecule. Tohoku J Exp Med 2012;228:325–32.
[91] Rodrigues L, Schmidt TP, Florenzano J, et al. PP54 – The slow-releasing hydrogen sulphide donor, GYY4137, exhibits novel anti-skin symptoms of psoriasis and related itch. Nitric Oxide 2015;47:S35–135.
[92] Matz H, Orion E, Wolf R. Balneotherapy in dermatology. Dermatol Ther 2003;16:132–40.
[93] Rodrigues L, Ekundi-Valentim E, Florenzano J, et al. Protective effects of exogenous and endogenous hydrogen sulfide in mast cell-mediated pruritus and cutaneous acute inflammation in mice. Pharmacol Res 2016;11:255–66.
[94] Kutz JL, Greaney JL, Santhanam L, et al. Evidence for a functional vasodilatatory role for hydrogen sulphide in the human cutaneous microvasculature. J Physiol 2015;593:2121–9.
[95] Olson KR. The therapeutic potential of hydrogen sulfide: separating hype from hope. Am J Physiol Regul Integr Comp Physiol 2011;301:R297.
[96] Chattopadhyay M, Kodela R, Nath N, et al. Hydrogen sulfide-releasing nsaids inhibit the growth of human cancer cells: a general property and evidence of a tissue type-independent effect. Biochem Pharmacol 2012;83:715–22.
[97] Wallace JL, Caliendo G, Santagada V, et al. Gastrointestinal safety and anti-inflammatory effects of a hydrogen sulfide-releasing diclofenac derivative in the rat. Gastroenterology 2007;132:261–71.