Hydrogen Sulfide Plays an Important Protective Role Through Influencing Endoplasmic Reticulum Stress in Diseases

Honggang Wang¹*, Xingzhuo Shi², Mengyuan Qiu¹, Shuangyu Lv¹, Huiyang Liu¹

1. Institute of Biomedical Informatics, Bioinformatics Center, School of Basic Medical Sciences, Henan University, Kaifeng, Henan, 475000, China
2. School of Life Science, Henan University, Kaifeng, Henan, 475000, China

*Corresponding Author

Honggang Wang E-mail: whg197167@vip.henu.edu.cn Tel.13663781967
Abstract: The endoplasmic reticulum is an important organelle responsible for protein synthesis, modification, folding, assembly and transport of new peptide chains. When the endoplasmic reticulum protein folding ability is impaired, the unfolded or misfolded proteins accumulate to lead to endoplasmic reticulum stress. Hydrogen sulfide is an important signaling molecule that regulates many physiological and pathological processes. Recent studies indicate that H₂S plays an important protective role in many diseases through influencing endoplasmic reticulum stress, but its mechanism is not fully understood. This article reviewed the progress about the effect of H₂S on endoplasmic reticulum stress and its mechanisms involved in diseases in recent years to provide theoretical basis for in-depth study.

KEYWORDS: Hydrogen sulfide; endoplasmic reticulum stress; cardiomyopathy; neurological diseases; respiratory diseases; vascular diseases

1. Introduction

The endoplasmic reticulum (ER) is an important organelle responsible for protein synthesis, modification, folding, assembly and transport of new peptide chains [1-5]. In addition, it regulates the cholesterol and lipid-membrane biosynthesis and the signaling mechanisms of cell surviving and death [6, 7]. Under stress conditions including glucose deficiency, environmental toxins, viral infection, changes in Ca²⁺ levels, hypoxia, inflammation and oxidative stress, ER homeostasis can be interrupted, which is termed ER stress (ERS). ERS is defined as the disturbance of ER function, which interferes with protein folding, post-translational modification and secretion. Finally, the accumulation of unfolded proteins in ER initiates a homeostatic signaling network called as the unfolded proteins reaction (UPR) [8, 9]. When the perturbation is moderate, UPR activation will promote a homeostatic recovery of ER and help cells adapt to changes. However, if the interference is intense and prolonged, ERS and UPR will initiate the death signaling pathway, which will lead to the onset of various diseases [10]. The ERS and UPR are mediated by three transmembrane ER signaling proteins: pancreatic endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6), which mediate three parallel signal branches respectively [11, 12]. Under non-pressure conditions, the binding immunoglobulin (BIP) binds to PERK, IRE1 and ATF6 to stabilize and prevent their
activation. The stressors and unfolded proteins promote the isolation of BIP from PERK, IRE1 and ATF6, thereby activating these three molecules. Subsequently, the autophosphorylated PERK phosphorylates eIF2a to inhibits mRNA translation and global protein synthesis, and increase ATF4 expression, the activated IRE1 cleaves Xbp1 mRNA and the isolated ATF6 is cleaved by 1-site protease (sp1) and 2-site protease (sp2) proteins in Golgi complex. At last, the cleaved Xbp1, the ATF4 and the spliced ATF6 promote the expression of ER chaperone genes, which are further involved in eliminating unfolded proteins and restoring homeostasis in normal cells (Figue 1) [10].

Many diseases have been reported to be related with ER stress [13, 14].

Hydrogen sulfide (H2S) has long been considered as a flammable, water-soluble, colorless and toxic gas. However, since the 1990s, more and more studies have confirmed that H2S belonged to a class of gasotransmitters, together with nitric oxide (NO) and carbon monoxide (CO) [15-17]. In mammalian cells, H2S is produced by endogenous enzymatic and non-enzymatic pathways. The enzymatic generation of H2S, which may be important for the regulation in given cells under special conditions, is the focus of the research. Several different mammalian enzymatic systems for H2S production have been described in detail. Most commonly, three typical H2S-producing enzymes are identified: cystathionine-gamma-lyase (CSE), cystathionine-beta-synthase (CBS) and 3-mercaptopyruvate thioredoxinase (3-MST) [18-20].

Cystathionine is produced by β-substitution reaction of homocysteine with serine catalyzed by CBS. CSE catalyzes the elimination of α, γ-cysteine of cystathionine to produce cysteine. Under the catalysis of CBS and CSE, cysteine can form H2S through β elimination reaction. 3-mercaptopyruvate (3-MP) is produced by transferring amines from cystine to α-ketoglutarate via cysteine aminotransferase (CAT). 3-MST catalyzes the sulphur of 3-MP to convert into H2S [21] (Figure 2). The biological function of H2S does not depend on H2S itself, but on the formation of new molecules, such as S-nitrosothiols, whose possible mechanisms include reversible protein sulfidation [22]. H2S has many physiological functions, such as relaxing blood vessels, lowering blood pressure [23, 24], anti-apoptotic [25], anti-inflammatory [26], anti-oxidative stress and regulation of ER stress [27]. The role of H2S in the regulation of ER stress has been one of the focuses of attention in recent years [28].
In this review, we summarize the progress about the effects of H\textsubscript{2}S on ERS and the mechanism involved in recent years to provide ideas for relevant basic research in the future.

2. H\textsubscript{2}S plays cardioprotective role by influencing endoplasmic reticulum stress

Diabetic cardiomyopathy (DCM) is one of the major cardiac complications independent of coronary artery disease and hypertension in diabetic patients [29]. In recent years, many studies have shown that ERS plays a crucial role in the occurrence and development of DCM [30, 31]. Hyperglycemia induces cardiomyocyte apoptosis by activating ERS through caspase-12 dependent pathway and C/EBP-homologous protein (CHOP) dependent pathway [32-34]. Fang Li and her coworkers reported that in streptozotocin (STZ)-induced diabetic rats, ERS was increased by hyperglycemia, leading to myocardial fibrosis and cardiomyocyte apoptosis. While treatment with H\textsubscript{2}S reduced ERS to inhibit myocardial apoptosis and improve myocardial fibrosis, suggesting that H\textsubscript{2}S had a potential role in the treatment of DCM [35]. In this experiment, since the intervention of H\textsubscript{2}S is simultaneous with the establishment of DC model, not after the establishment of DC model, thus, the protective effect of H\textsubscript{2}S on DC cannot be fully demonstrated.

Moreover, long-term hyperglycemia can cause excessive production of reactive oxygen species (ROS) in mitochondria of cardiomyocyte [36, 37] and excessive ROS induces ERS which leads to cardiomyocyte apoptosis [38]. H\textsubscript{2}S can inhibit the production of ROS, indicating that H\textsubscript{2}S can regulate ERS through ROS. ER and mitochondria are spatially close organelles which are joined together by ER-mitochondrial associated membranes [39]. ROS regulate ER-mitochondrial crosstalk during ERS-induced apoptosis [40]. In streptozotocin (STZ)-induced diabetic rats, H\textsubscript{2}S reduces ROS in mitochondria and ERS-induced myocardial apoptosis through regulating ER-mitochondrial crosstalk [41]. ROS associates the antioxidant effect of H\textsubscript{2}S with its inhibition of ER stress. Researches showed that the excessive lipid deposition and ERS might play a role in the pathogenesis of DCM [42-44]. In the hearts of STZ-induced rats or in AC16 cardiac cells treated with palmitic acid (PA), endogenous H\textsubscript{2}S decreased ERS, apoptosis and lipid accumulation increased, suggesting that endogenous H\textsubscript{2}S, ERS and lipotoxicity are involved in the pathological process of DCM. The further experiment showed that exogenous H\textsubscript{2}S alleviated myocardial lipotoxicity and ER stress. The similar results can be obtained by using ERS inhibitors (4-PBA), suggesting that exogenous H\textsubscript{2}S inhibits lipid accumulation and myocardial toxicity through
suppressing ERS [45]. This is consistent with previous reports that H₂S mitigated high fat diet-induced cardiac dysfunction through suppression of ERS [46]. The mechanism of the effect of ERS on myocardial lipotoxicity of DCM remains to be studied. Myocardial ischemia reperfusion (I/R) injury is an important cause of myocardial injury [47]. Recently, it has been proved that ERS is related to myocardial I/R injury [48]. Myocardial I/R decreased endogenous H₂S, increased ERS and ERS-induced cardiomyocyte apoptosis. H₂S preconditioning could reverse these above changes. Moreover, pretreatment with ERS inhibitors yielded similar results as H₂S. Collectively, these results indicated that H₂S ameliorated myocardial I/R injury by attenuating excessive ERS induced by myocardial I/R [49]. This added a new mechanism, which remains to be studied, to the myocardial protection of H₂S. Several studies suggest that chronic intermittent hypoxia (CIH) may induce ER stress and lead to myocardial injury [50-52]. Zhou, et al. reported that CIH induced myocardial injury by activating ERS, while the treatment with the inhibitor of cystathionine γ-lyase (DL-propargylglycine, PAG) alleviated myocardial injury induced by CIH [53]. This result is inconsistent with previous study that H₂S could alleviate myocardial injury in ischemia-reperfusion model [54]. The underlying mechanisms of the contradiction remain to be studied. It has been reported that post-conditioning (PC) inhibits apoptosis induced by I/R, however, its myocardial protection is lost in the elderly heart [55, 56]. Sun et al. reported that H₂S restored the cardioprotective effect of PC and reduced I/R-induced ERS, the similar effects were obtained by using 4-PBA, which indicated that exogenous H₂S restores PC-induced cardioprotection by inhibition of ERS in the aged cardiomyocytes [57] (table 1). Although there are many studies about the protective effect of H₂S on myocardium by influencing ER stress, the exact mechanism is not fully understood. Further researches are needed to provide a new way for the treatment of myocardial injury.

3. H₂S influences endoplasmic reticulum stress in neurological diseases

In recent years, there have been many reports that H₂S regulates ER stress to inhibit neurological diseases. Homocysteine (Hey), produced by demethylation of methionine [58], can induce ERS to lead the apoptosis of many types of neurons, including hippocampal and cortical neurons [59]. The research by Li et al. demonstrated that intraventricular injection of Hey
impaired learning and memory function, reduced the production of endogenous H$_2$S and increased the ERS of hippocampal cells, which suggested that Hcy-induced learning and memory loss was associated with reduced endogenous H$_2$S production and increased hippocampal ERS [60]. Similarly, the neurotoxicity to PC12 cells induced by arecoline is also involved with reduced endogenous H$_2$S production and increased hippocampal ERS [61]. Wei et al. reported that H$_2$S downregulated Hcy-induced neuronal ERS and upregulated the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus of rats. In addition, blocking BDNF-TrkB pathway by inhibitor could reverse the abovementioned effect of H$_2$S. Overall, these findings suggested that H$_2$S alleviated Hcy-induced neurotoxicity through reducing ERS by upregulating the BDNF-TrkB pathway [62]. In PC12 cells, H$_2$S also markedly inhibited homocysteine-induced ERS and increased the protein level of silent mating type information regulation 2 homolog 1 (SIRT-1) in the presence or absence of homocysteine treatment. Sirtinol, an inhibitor of SIRT-1, eliminated the inhibitory effect of H$_2$S on homocysteine-induced ERS, which indicated that H$_2$S protected PC12 cells against homocysteine-induced ER stress by upregulating SIRT-1 [63]. The similar results were obtained in vivo [64] Increasing evidences suggest that diabetes can cause cognitive impairment and memory loss [65, 66]. ERS-induced apoptosis in the hippocampus is the mechanism of diabetic cognitive impairment [67]. Wei et al. reported that H$_2$S improved cognitive impairment in diabetes mellitus by inhibiting ERS induced by hyperglycemia in hippocampus. Furthermore, the hippocampal endogenous H$_2$S generation of diabetic rats was decreased, while this downregulation is reversed by exogenous H$_2$S [68]. These results suggested that the neuroprotective effect of H$_2$S might be related to its promotion of endogenous H$_2$S production in hippocampal cells. However, it has been reported that the endogenous H$_2$S production in pancreas and liver of STZ-induced diabetic rats increased significantly [69]. This conflict is probably due to that the concentration of endogenous H$_2$S is diverse in different tissue. The mechanisms of H$_2$S regulating ERS to protect nerve injury need to be further studied. ERS will be a new target of treatment for neurological diseases.

Depression is a chronic and recurrent serious mental disorder characterized by loss of happiness, emotional disorders and suicidal tendencies. It affects more than 10% of the world’s population and causes a huge social burden [70, 71]. It has been reported that rats exposed to chronic unpredictable mild stress (CUMS) exhibited many behavioral and neurobiological
changes in depression [72]. The research demonstrated that CUMS induced depression-like behavior, caused hippocampal ERS in rats and suppressed the production of endogenous H₂S, while exogenous H₂S alleviated the above depression-like behavior suggesting that H₂S production disorder and ER stress in hippocampus played an important role in depressive behavior induced by CUMS [73]. The further studies showed that exogenous H₂S attenuated CUMS-induced depression-like behaviors by suppressing hippocampal ERS and increased the SIRT-1 expression in rats. Moreover, the inhibition of SIRT-1 by inhibitor reversed the protective effect of H₂S and promoted CUMS-induced ERS. Collectively, these indicated that H₂S inhibited CUMS-induced depressive-like behavior through suppressing CUMS-induced ERS by upregulating SIRT-1 pathway [74]. H₂S also exerts its protection against the neurotoxicity of formaldehyde through overcoming ERS via upregulation of SIRT-1 [75]. In addition to the SIRT-1 pathway, the BDNF/TrkB pathway is also related with the antidepressant effect of H₂S. BDNF is an important endogenous neurotrophic factor, mainly expressed in hippocampus and cortex [76]. H₂S mitigates CUMS-induced depressive-like behaviors, induces the expressions of BDNF and p-TrkB proteins and inhibits ERS in the hippocampus of CUMS-induced rats [77]. The inhibition of BDNF-TrkB pathway with K252a, an inhibitor of BDNF, reverses the protective role of H₂S in CUMS-induced depressive-like behaviors and hippocampal ERS, which indicates that H₂S plays an antidepressant-like effect through suppressing ERS via BDNF-TrkB pathway in CUMS-exposed rats [78](table 2). At present, the existing treatment of depression is often ineffective and can not completely solve the symptoms. With the in-depth study of the mechanism of H₂S antidepressant effect, the new H₂S-related drugs will be provided for the treatment of depression. ERS will also become a new target for the treatment of depression.

4. H₂S influences endoplasmic reticulum stress in respiratory diseases

Chronic obstructive pulmonary disease (COPD) can be defined as a disease characterized by exposure to harmful substances, leading to irreversible airflow restriction and shortness of breath [79, 80]. Evidences suggest that ERS may play an important role in the development or pathology of COPD [81, 82]. Cigarette smoke (CS) induces ER stress and ER stress-mediated apoptosis and suppresses the production of endogenous H₂S to lead COPD, which is reversed by exogenous H₂S [83]. Intraperitoneal injection of endogenous H₂S inhibitor in rat model of passive inhalation of CS aggravates these effects caused by CS, however, the ERS inhibitor suppress CS-induced
effects, which suggests that H₂S may inhibit CS-induced bronchial epithelial cell apoptosis through suppressing ERS [84]. Artery endothelial dysfunction induced by apoptosis of arterial endothelial cells is associated with the severity of COPD [85]. Exogenous H₂S reduces the apoptosis of pulmonary artery endothelial cells by suppressing ERS in a rat model of COPD [86]. The specific signaling pathways involved in the above effect need to be further studied. The decrease of ERS and endogenous H₂S are involved in the pathogenesis of acute lung injury (ALI). Exogenous H₂S can play protective role during the early stage of ALI by increasing ERS, which is contrary to the former statement [87]. The reason needs to be studied (table 3).

5. H₂S influences endoplasmic reticulum stress in vascular disease

Vascular calcification (VC) refers to the abnormal deposition of calcium and phosphorus minerals on the wall of blood vessels, ERS-induced apoptosis plays a vital role in the development of VC [88], so inhibiting apoptosis is an effective treatment for VC. Yang et al. reported that H₂S could inhibit VC and ERS of calcified aortic tissues. Furthermore, the ERS inducer Tm could block the ameliorated effect of H₂S on VC, while the effect of the ER stress inhibitor PBA on VC in rats treated with vitamin D3 plus nicotine was similar as that of H₂S. These indicated that H₂S ameliorated VC by suppressing ERS. Moreover, the protein levels of phosphorylated AKT and Akt were both upregulated by H₂S, suggesting that activation of the Akt signaling pathway is involved with the above effect of H₂S [89]. With the development of research, it will provide a new strategy and target for the prevention and treatment of VC. Endothelial dysfunction (ED) caused by inflammation is very important in the development of atherosclerosis (AS). Angiotensin II (AngII) is involved in the progression of ED, leading to atherosclerosis [90]. There is evidence that ERS and ED are the key factors leading to AngII-induced cytotoxicity [91, 92]. The results of Hu et al. revealed that AngII markedly induced cytotoxicity by promoting ERS and ED in human umbilical vein endothelial cells (HUVECs), which are reversed by H₂S supplementation via inhibiting NF-κB signaling pathway [93] (table 3). Similar results were obtained in other studies [94, 95]. Whether ERS can directly induce ED and the molecular mechanism of interaction between ER stress and ED need to be studied. With the deepening of the research, it will certainly provide a new prevention and treatment of AS.
6. Conclusion

ERS has been reported to be involved in many diseases and it is a “double-edged sword”: Acute ERS can reduce protein synthesis in ER, increase degradation of damaged and misfolded proteins and induce the production of protective proteins to alleviate stress-induced injury, while chronic ERS can induce caspase-12 dependent apoptotic pathway and C/EBP-homologous protein (CHOP) dependent apoptotic pathway to lead some diseases(Figure 3). So it is very important to study how to maintain ERS at an appropriate level. Although the mechanism of how prolonged ERS leads to disease is not fully understood, it is now clear that abnormal ER stress can cause disease by inducing excessive reactive oxygen species (ROS). The suppression of excessive ERS will provide a way to prevent and treat many diseases. H2S has been shown to play a protective role in many diseases by inhibiting ERS, but individual research has reported that H2S inhibits diseases by promoting ERS, perhaps the reason is that the basic level of ERS varies in different tissues or different diseases have different effects on ERS. The mechanism of H2S regulating ERS in diseases needs further study. In conclusion, ERS may be a potential target for H2S therapy with the in-depth study of the effect of H2S on ERS.

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Conflict of Interest statement
The authors declare that there are no conflicts of interest.

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Table 1. H2S plays cardioprotective role by influencing endoplasmic reticulum stress

| Experimental models | Effects | Proposed mechanisms | References |
|---------------------|---------|---------------------|------------|
| streptozotocin(STZ)-induced diabetic rats | Intraperitoneally administration of NaHS at 30 µmol/kg or 100 µmol/kg for 8 weeks could improve myocardial hypertrophy and myocardial collagen deposition in hearts of diabetic rats | Suppressing STZ-induced ER S | [35] |
| AC16 cardiac cells treated with palmitic acid(PA) | Pretreatment AC16 cells with 100 µmol/L of NaHS could suppress the PA-induced myocardial injury | Suppressing PA-induced ER S | [45] |
| a murine model of high fat diet (HFD)-induced cardiomyopathy | H2S therapy mitigated high fat diet-induced cardiac dysfunction | Suppressing cardiac ER S induced by HFD feeding. | [46] |
| Model of | H2S preconditioning significantly | Attenuating ER-induced ER S | [49] |
**Table 2. H₂S influences endoplasmic reticulum stress in neurological diseases**

| Experimental models                                      | Effects                                                                 | Proposed mechanisms                                                                 | References |
|-----------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------|
| Adult male SD rats were intracerebroventricularly (icv) injected with Hcy | H₂S alleviated Hcy-induced neurotoxicity                                | Inhibiting ERS by upregulating the BDNF-TrkB pathway                                | [62]       |
| homocysteine-treated PC12 cells                           | exogenous H₂S significantly attenuated the homocysteine-induced ERS response in hippocampal. | By upregulating SIRT-1                                                             | [63]       |
| streptozotocin-induced diabetic rats                      | H₂S improved cognitive impairment in diabetes mellitus                  | Suppression in hippocampal endoplasmic reticulum stress induced by hyperglycemia    | [68]       |
| rat model of chronic unpredictable mild stress           | H₂S inhibited CUMS-induced depressive-like behavior.                    | Suppressing CUMS-induced ERS by upregulating sirt-1 pathway                         | [74]       |
| Formaldehyde (FA)-induced PC12 cells                     | H₂S exerts its protection against the neurotoxicity of FA.             | Through overcoming ERS via upregulation of SIRT-1                                   | [75]       |
Table 3. H$_2$S influences endoplasmic reticulum stress in respiratory diseases and vascular disease

| Experimental models | Effects | Proposed mechanisms | References |
|---------------------|---------|---------------------|------------|
| Sprague-Dawley rats exposed to cigarette smoke (CS) generated from 20 commercial unfiltered cigarettes for 4 h/day, 7 days/week for 4 months | NaHS significantly inhibited inhibit CS-induced bronchial epithelial cell apoptosis in rat lungs | Inhibiting ERS | [84] |
| Rat model of chronic obstructive pulmonary disease established by means of passive smoke exposure and intratracheal injection with lipopolysaccharide (LPS) | Exogenous H$_2$S reduces the apoptosis of pulmonary artery endothelial cells | Suppressing ERS | [86] |
| Rats with acute lung injury (ALI) induced by oleic acid (OA) | H$_2$S could promote alveolar epithelial cell endoplasmic reticulum stress in rats with ALI. | | [87] |
| Vitamin D3 plus nicotine (VDN) model of rats | H$_2$S alleviates vascular calcification (VC) and phenotype transformation of vascular smooth muscle cells. | Inhibiting ERS via activation of the Akt signaling pathway | [89] |
| 10-6 M AngII treated human umbilical vein endothelial cells (HUVECs) | H$_2$S supplementation angiotensin II-stimulated endothelin-1 generation and | via inhibiting NF-$\kappa$B signaling pathway | [93] |
Akt: serine threonine kinase; NF-κB: nuclear factor kappa-B

**Figure 1. Summary of ERS and the UPR.**

When ERS is activated, there are three parallel signaling branches in UPR. ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; BIP, binding immunoglobulin protein; ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; IRE1, inositol-requiring protein 1; PERK, PRKR-like ER kinase; SP1, site-1 protease; UPR, unfolded protein response; XBP1, X-box binding protein 1
Figure 2. Summary of the production process of endogenous H₂S
CBS: cystathionine-beta-synthase; CSE: cystathionine-gamma-lyase; 3-MST: 3-mercaptopuruvate thiotransferase; 3-MP: 3-mercaptopuruvate; CAT: cysteine aminotransferase

Figure 3. Summary of the role of endoplasmic reticulum stress
ERS: endoplasmic reticulum stress; CHOP: C/EBP-homologous protein