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Regulation of Cystathionine γ-Lyase Expression in the Cardiovascular System: Insights into Exogenous Hydrogen Sulfide, Hydrogen Peroxide, Hypoxia, and Nuclear Factor kB Signaling

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ABSTRACT

Cystathionine γ-lyase is a key enzyme in the transsulfuration pathway responsible for endogenous hydrogen sulfide production in the cardiovascular system. As the third gaseous signaling molecule, hydrogen sulfide plays crucial roles in maintaining vascular homeostasis, regulating vasodilation, and protecting against ischemia-reperfusion injury. This review comprehensively analyzes the regulatory mechanisms governing cystathionine γ-lyase expression under various physiological and pathological conditions. Exogenous hydrogen sulfide exhibits concentration-dependent bidirectional regulation of cystathionine γ-lyase expression, with lower concentrations (10-80 μ M) suppressing cystathionine γ-lyase through feedback inhibition, while higher concentrations (120-160 μM) upregulating its expression as a protective response. Hydrogen peroxide , at moderate concentrations (5 μM), significantly enhances cystathionine γ-lyase promoter activity and mRNA/protein expression, suggesting a potential feedback loop where cystathionine γ-lyase -derived hydrogen sulfide scavenges reactive oxygen species. Hypoxia regulates cystathionine γ-lyase through transcriptional and post-transcriptional mechanisms, with increased cystathionine γ-lyase expression potentially protecting cells by elevating hydrogen sulfide levels and buffering oxygen consumption. Furthermore, lipopolysaccharide-induced cystathionine γ-lyase expression critically depends on the Nuclear Factor κB transcription factor binding site (GGACATTCC) within the cystathionine γ-lyase promoter, establishing a direct link between inflammatory signaling and hydrogen sulfide biosynthesis. Based on these findings, we propose a mechanistic hypothesis wherein hypoxia-induced cardiomyocyte apoptosis releases hydrogen peroxide, which activates Nuclear Factor κB signaling in vascular endothelial cells to upregulate cystathionine γ-lyase expression, leading to enhanced hydrogen sulfide production and subsequent vasodilation. Understanding these regulatory networks provides theoretical foundations for developing therapeutic strategies targeting the cystathionine γ-lyase/hydrogen sulfide pathway in cardiovascular diseases, including myocardial infarction, hypertension, and atherosclerosis.

Keywords: Cystathionine γ-lyase; Hydrogen sulfide; Hypoxia; Nuclear Factor κB; Cardiovascular regulation

1. Introduction

Hydrogen sulfide (H_2S), a well-known toxic gas, has recently been recognized as the third endogenous gaseous signal molecule in recent years. Cystathionine γ-lyase (CSE), one of the three enzymes in the transsulfuration pathway, is responsible for synthesizing endogenous H_2S using L-cysteine or L-homocysteine as a substrate [1,2]. The production of CSE mRNA must occur in the rat aorta in association with H_2S provided with exogenous L-cysteine. Typically, cystathionine β-synthase (CBS) plays a crucial role in developing and maintaining the central nervous system, and the radial glia/astrocyte dysfunction may be involved in the complex neuropathological features [3]. Moreover, 3-mercaptopyruvate sulfurtransferase (3MST), another H_2S-producing enzyme, is localized to brain neurons and the vascular endothelium [4]. The vascular smooth muscle cells (SMCs) from the CSE gene knockout mice are more susceptible to apoptosis induced by exogenous H_2S at physiologically relevant concentrations [5]. H_2S-induced S-sulfhydration on proteins are potential novel targets for therapeutic intervention and drug design for the skin, which may lead to the development and application of H_2S-related drugs for dermatological diseases [6]. Since H_2S has been explored to exhibit a wide range of physiologic functions to maintain vascular homeostasis, it is not surprising that H_2S may play beneficial effects in the progression of atherosclerosis [7]. In-depth research on the regulation of CSE gene expression can not only clarify the molecular mechanism of the occurrence of related diseases but also discover how different exogenous factors regulate CSE gene expression, and it is likely to find the molecular mechanism of the occurrence of related diseases and current targets of drug action.

2. Regulation of Cystathionine γ-lyase Expression by Exogenous Hydrogen Sulfide

The protective effect of exogenous H_2S at low concentrations (30 or 50μM) on rat aortic SMCs against cytotoxicity and damage induced by homocysteine has been demonstrated, resulting in enhanced cell viability [8]. Conversely, upregulation of CSE leads to SMC apoptosis due to an elevation in endogenous H_2S production [9]. Moreover, mice with cardiac overexpression of CSE exhibit significant resistance against ischemia-reperfusion injury. This protection is accompanied by reduced myocardial inflammation and preserved mitochondrial function [10]. After suppressing the endogenous background expression of CSE, direct administration of exogenous H_2S at a concentration of 100 μM can induce apoptosis in human aortic SMCs. The activity of CSE has been reported to be regulated by Calmodulin in the presence of 1-2 mM Ca^{2+} [11]. Vascular SMCs from CSE gene knockout mice are more susceptible to apoptosis induced by physiologically relevant concentrations of exogenous H_2S [5]. Treatment with low levels of exogenous H_2S (≤ 100 μM) can protect cells from radiation damage [12]. However, further investigation is necessary to conclusively determine whether CSE is regulated by Ca^{2+}/Calmodulin [2]. GYY4137 (a slow-releasing H_2S donor) may serve as a novel therapeutic tool for preventing diabetes-associated vascular dysfunction [13].Modulating H_2S signaling represents a potential novel therapeutic approach for managing hypertension; however, additional experimental and clinical studies on the role of H_2S in hypertension are required [14].

Cystathionine γ-lyase mainly mediates the endogenous generation of H_2S in the cardiovascular system [15]. After inhibiting endogenous background CSE expression, the direct administration of 100 μM exogenous H_2S can induce the apoptosis of human aorta smooth muscle cells [9]. Mice overexpressing CSE in the heart exhibit resistance to ischemia-reperfusion

injury, and this protection is accompanied by a decrease in myocardial inflammation [10]. Vascular smooth muscle cells (VSMCs) from CSE gene-knockout mice are more susceptible to apoptosis induced by exogenous H_2S at physiologically relevant concentrations than those from wild-type mice [5]. Hydrogen sulfide is synthesized within the vasculature and facilitates vascular homeostasis, vasodilation, and endothelial cell proliferation [16]. Elevated levels of homocysteine induce dysfunction in endothelial cells, while the metabolic and physiological functions of H_2S enable it to function as a protective agent [17]. Hydrogen sulfide is recognized as both a signaling molecule and cytoprotectant that safeguards various tissues and organs against oxidative stress and ischemia-reperfusion injury [18]. Endogenous H_2S plays modulatory roles in hypoxia-induced cardiovascular responses by inhibiting spontaneously hypertensive (SH) rats [19]. The production of H_2S primarily through endothelial CSE contributes to cardiovascular homeostasis [20].

Several studies have investigated the effects of H_2S in human vessels. Hydrogen sulfide-induced relaxation has been demonstrated in internal mammary [21], pulmonary [22], mesenteric [23], and intrarenal arteries [24] as well as in perfused human placentas [25]. Upregulation of CSE expression during hypoxia may increase the production and concentration of H_2S in cells and protect cells from hypoxia[26]. A controlled release formulation of S-propargyl-cysteine exerted protective effects against myocardial infarction (MI) via the CSE/H_2S pathway [27]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 is a positive transcriptional regulator of CSE in endothelial cells, and some researchers propose that it may modulate the production of endogenous H_2S [28]. Cystathionine γ-lyase-derived H_2S production by endothelial cells is critical for maintaining endothelial function and exercise capacity and protecting against myocardial ischemia/reperfusion injury [29].

An in vitro study showed that an exogenous H_2S donor attenuated hypoxia-induced apoptosis in primary rat nucleus pulposus (NP) cells [30]. Hydrogen sulfide has been identified as an excitatory mediator of hypoxic sensing in carotid bodies [31]. Incubation with sodium hydrosulfide (NaHS), an H_2S donor, increased the expression of miR-21 and attenuated the reduced cell viability and increased apoptosis caused by ischemia-reperfusion (I/R) in Buffalo rat liver (BRL) cells [32]. The exogenous administration of NaHS might be a potential strategy for treating nickel-induced lung cancer progression [33]. Pretreatment with NaHS or aspirin (ATB-340) in aged rats fed a high-fructose diet (HFD) and animals exposed to water-immersion restraint stress (WIRS) attenuated gastric damage compared to vehicle treatment [34].

Some studies have demonstrated that appropriate levels of exogenous H_2S can impact the regulation of cystathionine gamma-lyase (CSE) expression. The application of exogenous H_2S at concentrations of 50, 100, and 200 μM can reduce the action potential duration in healthy papillary muscles. Moreover, pretreatment with glibenclamide partially attenuates the effects induced by 100 μM exogenous H_2S [35]. Exposing mammalian cells to exogenous H_2S within a range of 10-80 μM downregulates both transcription and expression levels of CSE. Conversely, an exposure to exogenous H_2S at a concentration of 120 μM significantly increases CSE transcription and expression [36]. Additionally, hypoxia has been found to upregulate CSE expression to some extent [26]. Therefore, it is crucial to investigate how exogenous H_2S regulates CSE expression in vascular endothelial cells during hypoxia. In this study, we examined the effects of applying 100 μM exogenous H_2S on CSE expression in human umbilical vascular endothelial cells (HUVECs) under hypoxic conditions.

Since the higher concentration of exogenous H_2S is very harmful to cells [37], the down-regulation of exogenous H_2S at 160 μM on CSE expression is perhaps unavoidable. Moreover, exogenous H_2S

(100μM) can alone inhibit HEK-293 cells proliferation [38]. Exogenous H_2S could suppress CSE expression concentration-dependently while exogenous H_2S changed from 10 to 80 μM. In the concentration range, exogenous H_2S might be feedback inhibition of CSE expression. The up-regulation of CSE expression may be derived from the protective effect of endogenous H_2S on cells at the higher concentration (from 120 to 160 μM) of exogenous H_2S [36]. Hydrogen sulfide donor sulforaphane (SFN) reshapes the CBS-H_2S signaling axis, activates mitochondrial autophagy, and suppresses inflammation, offering novel insights into multi-target therapeutic approaches for Parkinson's disease (PD) and underscoring the essential role of H_2S in neuroprotection[39].

There is no doubt that the CSE expression can respond specifically to exogenous H_2S within a certain concentration range. The up-regulation of CSE expression may be attributed, in part, to the detrimental effects of higher concentrations of exogenous H_2S on mammalian cells. CSE expression exhibits feedback regulation at lower concentrations of exogenous H_2S and can be upregulated at higher concentrations, while emphasizing that exceeding a certain level of exogenous H_2S concentration could pose harm to biological macromolecules.

3. Cystathionine γ-Lyase Expression Is Regulated by Exogenous Hydrogen Peroxide

Since H_2S is a reducing agent that readily reacts with hydrogen peroxide (H_2O_2), endogenous H_2S may scavenge reactive oxygen species (ROS). A state of moderately increased levels of intracellular ROS is referred to as oxidative stress such as H_2O_2. Although it can cause pathological damage, both H_2O_2 and endogenous H_2S also function in normal cell regulation [40,41]. Endogenous H_2S acts as a reducing agent that readily reacts with H_2O_2 and scavenges ROS [42] Administration of exogenous H_2S effectively protects myocytes and contractile activity by scavenging ROS [43] and accelerates the removal of H_2O_2 generated by homocysteine in isolated mitochondria[44]. The administration of H_2O_2 restored enzyme activity levels and accelerated the elimination of both H_2O_2 and superoxide anion generated by homocysteine in isolated mitochondria [44]. Moreover, hydrogen peroxide protects neurons from oxidative stress by increasing the production of the antioxidant glutathione [42], while also safeguarding cells against oxidative injury induced by H_2O_2 [45,46].

Hydrogen sulfide synthesis is downregulated in the rostral ventrolateral medulla (RVLM)/Botzinger complex during hypoxia, and H_2S synthesis is diminished in the RVLM, facilitating hypothermia during hypoxia [47,48]. H_2S protects cells against H_2O_2-induced oxidative injury [45,46] and exerts its cytoprotective effect by increasing GSH production and scavenging ROS [49]. Hydrogen sulfide has been identified as an excitatory mediator of hypoxic sensing in carotid bodies [31]. Hydrogen sulfide-induced gastroprotection against I/R-injury is due to increased gastric microcirculation and antioxidative properties [29]. Hydrogen sulfide increases the generation of ROS in the carotid body enhances the chemosensory reflex, triggers hypertension[50], is an extremely reactive molecule, and may efficiently react with other compounds, especially reactive oxygen and nitrogen species [51]. Exogenous H_2S donor attenuated hypoxia-induced apoptosis in primary rat nucleus pulposus (NP) cells (Sun, Qi et al. 2018). Incubation with Na_2S [30]. Incubation with NaHS increased the expression of miR-21 and attenuated the reduced cell viability and increased apoptosis caused by ischemia-reperfusion (I/R) in buffalo rat liver (BRL) cells [32]. Oxidative stress injury in I/R injury rats with CSE knockout was aggravated, while the increased expression of H_2S and CSE in the aortic tissues alleviated the oxidative stress injury [52]. Unexpected relationship between oxidative stress homeostasis and H_2S overproduction in Down Syndrome (DS), extending beyond human chromosome 21 (Hsa21) trisomy[53].

The effect of exogenously applied H_2O_2 on CSE expression in several mammalian cell lines demonstrates that exogenously applied H_2O_2 regulates CSE genes at promoter mRNA and protein levels. In particular, it is noteworthy that the treatment of a medium concentration (5 μM) of H_2O_2 at a longer time (1.5 h) upregulated CSE expression in the mammalian cells at levels of the promoter, mRNA, and protein[54]. It can be speculated that the up-regulation of CSE expression induced by exogenous H_2O_2 may contribute to the increase in production and concentration of endogenous H_2S, which partially scavenges ROS like H_2O_2 in mammalian cell. Collectively, exogenously applied H_2O_2 significantly affects CSE mRNA and protein expression and affects CSE promoter activity in mammalian cells. Exogenous H_2O_2 can up-regulate the expression of the CSE gene in mammalian cells, which would open the possibility of indirect scavenging effects of the CSE gene on ROS in mammalian cells.

4. Regulation of Cystathionine γ-lyase Expression by Hypoxia

An adequate supply of O_2 is essential for the survival of the mammalian cells, and hypoxia profoundly impacts physiological systems [55]. The H_2S-induced animation-state can protect mice from lethal hypoxia [55,56], and the anti-ischemic protection can be achieved by applying exogenous H_2S and up-regulating the endogenous production of H_2S [57]. The regulatory effects of H_2S have been shown to modulate neuronal activity, relax smooth muscle, regulate insulin release, induce angiogenesis, suppress inflammation and protect cells [58]. Reduced H_2S production mediated hypo-adrenocortical responsiveness and NLRP3 inflammasome activation during hypoxia [59].

The cystathionine γ-lyase/hydrogen sulfide pathway is indirectly linked to hypoxia, and H_2S protects mammalian cells against hypoxia-induced injury. Hydrogen sulfide is the physiologic gas transmitter of the carotid body and enhances its sensory response to hypoxia [60], and is also an essential mediator of the hypoxic response in a variety of O_2-sensitive tissues [61,62]. Sodium hydrosulfide administration reduced myocardial infarct size and prevented cardiomyocyte apoptosis [63], and S-propargyl-cysteine has cardioprotective properties in myocardial infarction rats and preserved cell viability when cultured cells were exposed to hypoxia [64]. Experiments using cultured cardiomyocytes suggested hypoxia causes apoptosis, and apoptosis may play essential roles in ischemic heart diseases [65], and increased tissue content of H_2S protects the heart from ischemia/reperfusion damage [57]. Hydrogen sulfide protects human skin keratinocytes against $CoCl_2$-induced injuries [66]. Cystathionine γ-lyase transcription undergoes a period of repression and recovery, while CSE mRNA and protein levels increase during hypoxia [2]. Hydrogen sulfide has the potential to restore aging-induced loss of cardioprotective effects of RIPC by up-regulating HIF-1alpha/Nrf2 signaling [67].

Cystathionine γ-lyase can respond to hypoxia through transcriptional and post-transcriptional regulation, and hypoxia can up-regulate CSE expression to some extent. Thus, the up-regulation of CSE expression during hypoxia may help increase the production and concentration of H_2S in mammalian cells, indirectly protecting cells from hypoxia. The author would like to propose a hypothesis that the up-regulation of CSE in mammalian cells may partially protect cells from lethal hypoxia, probably by increasing the H_2S content, buffering oxygen consumption within mammalian cells. Recently, The administration of exogenous H_2S further diminished CSE expression at various time points in HUVECs under hypoxic conditions. Technical terms were defined based on their initial applications. These findings strongly suggest that vascular endothelial cells respond to fluctuations in blood H_2S levels during oxygen-deficient periods[68].

5. Nuclear Factor κB Transcription Factor Binding Site on Cystathionine γ-lyase Promoter Is Critical for LPS-Induced CSE Expression

The generation of CSE mRNA must occur along with H_2S in the rat aorta [69,70] provided with exogenous L-cysteine. The CSE/H_2S signaling pathway is involved in the inflammation induced by endotoxins such as lipopolysaccharides (LPS). The inhibitory effects of LPS on endothelium-dependent relaxation results in pulmonary hypertension might also be mediated by H_2S [71]. Pulmonary surfactant (PS) decrease is the essential physiopathologic process of acute lung injury (ALI) induced by LPS. Exogenously applied H_2S can attenuate the process of ALI that likely because H_2S can adjust the composing and secretion of PS [72]. Hydrogen sulfide may represent a novel endogenous mechanism of cytoprotection in the inflamed joint, suggesting a potential opportunity for therapeutic intervention [73]. Sodium hydrosulfide dose-dependently inhibited LPS-induced chemokine receptor C-X3-C motif chemokine receptor 1 expression in macrophages [74]. Hydrogen sulfide breathing prevents inflammation and improves survival after the LPS challenge by altering sulfide metabolism in mice [75]. Ralph A. Weinberg 264.7 murine macrophages treated with LPS mediated early apoptosis through TNF-alpha and the late apoptotic events through the production of H_2S [76]. Endogenous H_2S deficiency contributed to sepsis-induced myocardial dysfunction (SIMD) and exogenous H_2S ameliorated sepsis-induced myocardial dysfunction by suppressing inflammation and endoplasmic reticulum stress (ERS) via inhibition of the TLR4 pathway [77]. Deodorized garlic (DG) treatment decreases heart damage caused by LPS through the cross-talk between the H_2S and NO systems[78]. Hydrogen sulfide inhibits the proliferation of A1 astrocytes induced by LPS-based neuroinflammation following cerebral I/R and promotes the transformation of astrocytes into A2 subtype, which may be related to up-regulation of the large-conductance calcium- and voltage-activated K^+ channel (BK_{Ca}) [79]. Protective effects of Alpha-lipoic acid (ALA) are dependent on the reduction in CSE expression in LPS-stimulated RAW 264.7 macrophages[80].

Nuclear Factor κB is a heterodimer involving a variety of signaling pathways [81]. The transcription factor NF-κB regulates inflammatory responses by inducing the expression of various genes [82]. The NF-κB pathway can be rapidly activated by a large spectrum of chemically diverse agents and stress conditions, including bacterial LPS, microbial and viral pathogens, cytokines and growth factors [82].Hydrogen sulfide can inhibit NF-κB activation in LPS-stimulated macrophages [83]. An increase in plasma H_2S concentration alongside augmented liver H_2S biosynthesis from exogenous cysteine is also apparent in animals four h after LPS injection [84,85]. Serine (Ser) 276 phosphorylation of p65 is increased by LPS-mediated PKA (Protein kinase A) activation in Raw 264.7 murine macrophages [86]. Secreted protein acidic and rich in cysteine (SPARC) afford beneficial actions in inhibitions IκB-alpha degradation and phospho-transcription factors of the nuclear factor κB p65 activation induced by LPS [87]. Secreted protein acidic and rich in cysteine (SPARC) produces anti-inflammatory effects in LPS-stimulated H9c2 cells partly through the CSE/H_2S pathway by impairing IkappaB-alpha/NF-κB signaling [88]. 4-trifluoromethylquinoline derivative (TKL002) exerts potent antiglioblastoma activity via modulation of the CTH/H_2S/NF κB/epithelial-mesenchymal transition (EMT) signaling axis, highlighting its potential as a quinoline-based therapeutic candidate to overcome intrinsic glioblastoma (GBM) resistance and invasiveness[89].

Cystathionine γ-lyase / hydrogen sulfide signaling pathway is involved in the inflammation induced by endotoxins such as LPS [73,83,87,88,90,91]. The transcriptional and post-transcriptional regulation of the CSE gene was involved in the NF κB transcription factor binding site on the promoter in the mammalian cells under the treatment of LPS.

Some studies have indicated that H_2S plays an essential role in inflammation, and LPS stimulates the expression of the CSE gene and H_2S production rate [92]. Hydrogen sulfide regulates LPS-induced inflammation and apoptosis by activating the PI3K/Akt/NF κB signaling pathway [93]. The source of H_2S, either endogenous (via CSE) or exogenous (via GYY4137), supports or inhibits the LPS-induced NF-κB activity and Glut1 expression, respectively [94].

Exogenous H_2S inhibits wound-induced macrophage activation via the NF-κB pathway, and appropriate H_2S supplementation may help control inflammation [95]. SPRC exerts an anti-inflammatory effect in LPS-stimulated rat cardiomyocyte H9c2 cells partly through the CSE/H_2S pathway impairing IκB- α /NF-κB signaling [88]. Lipopolysaccharide increases the biosynthesis of CSE and H_2S in macrophages, mainly in a TLR-4- and NF κB-dependent manner [96]. Sodium hydrosulfide (an H_2S donor) suppresses the degradation of IκB-alpha and the activity of NF-κB [97]. Endogenous H_2S inactivates IKK beta to inhibit the NF-κB pathway and control pulmonary artery endothelial cell (PAEC) inflammation [98]. tumor necrosis factor-α alpha affects CSE gene expression, such that vascular endothelial cells respond to TNF alpha in the blood by regulating CSE expression. The regulatory mechanisms associated with the effects of TNF-α on the transcriptional regulation of the CSE gene in HUVECs and the NF-κB pathway warrant further investigation[99].

Exogenous H_2S attenuates angiotensin II-induced inflammation and cytotoxicity by inhibiting the ET1/NF-κB signaling pathway in HUVECs [100]. The effects of H_2S on the modulation of smooth muscle relaxation, inflammation suppression, and cell protection have been extensively studied [101], and the CSE/H_2S signaling pathway is involved in the inflammation induced by endotoxins, such as LPS. The NF-κB-binding site in the CSE promoter is critical for LPS-induced CSE expression in mammalian cells [92]. Moreover, the CSE/H_2S system protects against LPS-induced inflammation and cell hyperpermeability by blocking NF-κB transactivation[102]. Lipopolysaccharide -induced inflammation in murine macrophages is associated with H_2S production, and CSE/H_2S attenuates LPS-induced sepsis by inhibiting oxidative stress [76,103]. Exogenous H_2S ameliorates intestinal injury by downregulating inflammation and activation of autophagy, suggesting the potential of NaHS as a therapeutic agent for ulcerative colitis (UC) [104]. Methionine restriction (MR) attenuated LPS-induced lung injury through CSE and H_2S modulation [105].

Lipopolysaccharide could significantly increase the expression levels of mRNA and protein of the CSE gene after J774.1A cells and RAW264.7 cells under the treatment of LPS for 6 h [92]. Since LPS affected the post-transcriptional regulation of the CSE gene, there may be the NF-κB transcription factor binding site on the promoter of the CSE gene in the mammalian cells. The DNA sequence GGACATTCC on the promoter of the CSE gene has been heavily associated with transcriptional regulation of the CSE gene in mammalian cells undergoing LPS therapy. The NF-κB transcription factor on the CSE promoter is critical for LPS-induced CSE expression in mammalian cells.

6. Conclusion

Cystathionine γ-lyase is the dominant enzyme responsible for the production of endogenous H_2S in the cardiovascular system, where hypoxia is one of the pathogenic conditions regularly encountered. Hypoxia-regulated CSE expression in mammalian cells is complex, with CSE transcription undergoing periods of repression and restoration, while total mRNA and protein levels increase during hypoxia. Based on the above analysis, we proposed a hypothesis about the mechanism of CSE protection on the myocardial cells (Figure 1), and this assumption explains the mechanism as follows. Under hypoxic conditions, apoptosis is induced in some cardiomyocytes, a process that releases H_2O_2 into vascular endothelial cells in the minor arteries of the heart.

Proper concentrations of H_2O_2 promote the resumption of CSE expression in vascular endothelial cells via NF-κB signaling pathway. The up-regulation of CSE expression in vascular endothelial cells produces additional hydrogen sulfide H_2S, which accelerates vasodilation in SMCs.

The CSE gene is primarily expressed in the cardiovascular system. Its close relationship to the occurrence of cardiovascular disease suggests that the study of the regulatory mechanisms of CSE gene expression has significant theoretical and clinical value in the study of cardiovascular disease. Through the analysis of the CSE gene and its promoter in different populations, if it can be confirmed at the molecular level that some cardiovascular diseases, such as myocardial infarction, are caused by abnormalities of the CSE gene and its promoter, it can provide new ideas for effective screening and active intervention treatment of some cardiovascular diseases.

Figure 1

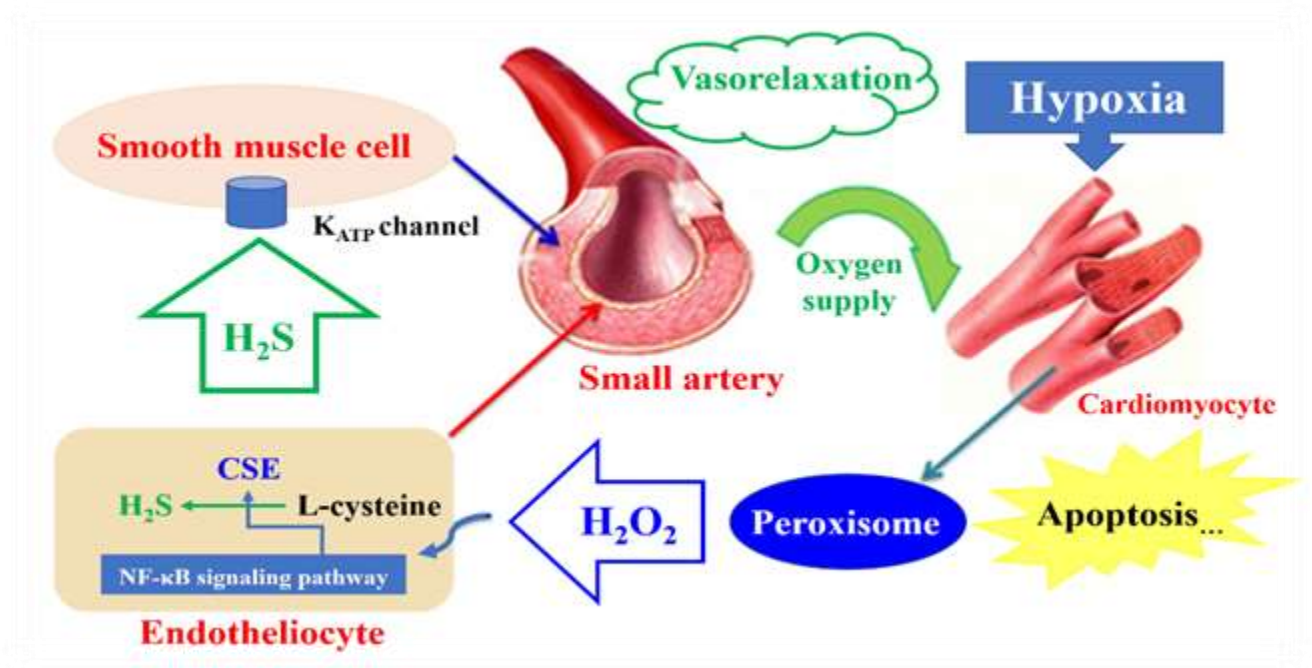

Figure 1 Legends

A hypothesis on the mechanism of cystathionine **γ**-Lyase protection of myocardial cells during hypoxia. Under hypoxia, cardiomyocyte apoptosis releases H_2O_2 into vascular endothelial cells, where appropriate levels restore CSE expression via NF-κB signaling. The resulting H_2S promotes vasodilation of smooth muscle cells, improving circulation—this increases cardiac oxygen supply, reduces infarct size, and attenuates apoptosis

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Maoxian Wang made the contributions to this study, writing, reviewing and approving the final version of the manuscript alone.

Ethics approval and consent to participate

Not applicable.

Conflict of interest statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Additional files

Not appliable

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