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Invited critical review

Hydrogen sulfide as a potent cardiovascular protective agent

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ABSTRACT

Hydrogen sulfide (H_2S) is a well-known toxic gas with the characteristic smell of rotten eggs. It is synthesized endogenously in mammals from the sulfur-containing amino acid L-cysteine by the action of several distinct enzymes: cystathionine-γ-lyase (CSE), cystathionine-ß-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (3-MST) along with cysteine aminotransferase (CAT). In particular, CSE is considered to be the major H_2S-producing enzyme in the cardiovascular system. As the third gasotransmitter next to nitric oxide (NO) and carbon monoxide (CO), H_2S plays an important role in the regulation of vasodilation, angiogenesis, inflammation, oxidative stress and apoptosis. Growing evidence has demonstrated that this gas exerts a significant protective effect against the progression of cardiovascular diseases by a number of mechanisms such as vasorelaxation, inhibition of cardiovascular remodeling and resistance to form foam cells. The aim of this review is to provide an overview of the physiological functions of H_2S and its protection against several major cardiovascular diseases, and to explore its potential health and therapeutic benefits. A better understanding will help develop novel H_2S-based therapeutic interventions for these diseases.

Contents

Abbreviations: H_2S, hydrogen sulfide; NO, nitric oxide; CO, carbon monoxide; CHD, coronary heart disease; PAH, pulmonary arterial hypertension; I/R, ischemia/reperfusion; CSE, cystathionine-γ-lyase; CBS, cystathionine-ß-synthase; 3-MST, 3-mercaptopyruvate sulfurtransferase; CAT, cysteine aminotransferase; K_{ATP}, ATP-sensitive potassium; SUR1, sulfonylurea receptor 1; VSMCs, vascular smooth muscle cells; PI3K, phosphatidylinositol 3-kinase; VEGF, vascular endothelial growth factor; ERK1/2, extracellular signal-regulated kinase 1/2; NF-κB, nuclear factor-κB; HIF-1α, hypoxia-inducible factor 1α; PIP3, phosphatidylinositol-3,4,5-trisphosphate; ROS, reactive oxygen species; redox, reduction/oxidation; Nrf2, nuclear factor erythroid 2-related factor 2; JNK, c-Jun N-terminal kinase; oxLDL, oxidized low-density lipoprotein; PAG, DL-propargylglycine; Ang II, angiotensin II; HO-1, heme oxygenase-1; DATS, diallyl trisulfide.

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1. Introduction

Hydrogen sulfide (H_2S) is a colorless, flammable and water-soluble gas characterized by a peculiar smell of rotten eggs. The toxic actions of H_2S have been known for more than 300 years. H_2S has long been regarded as only an environmental hazard, but recently it is thought to be the third gaseous signaling molecule after nitric oxide (NO) and carbon monoxide (CO). Similar to NO and CO, H_2S is synthesized in many different cell types and can easily diffuse without involvement of any transporters. Thus, it is not surprising that this gas has multiple biological actions including vasodilation, pro-angiogenic effect, pro- and anti-inflammatory properties, resistance to oxidative stress as well as pro- and anti-apoptotic activities [1,2]. There is growing evidence that H_2S is a critical regulator of cardiovascular functions and plays a protective role in the pathogenesis and development of cardiovascular diseases, a leading cause of morbidity and mortality worldwide [3]. In the present review, we summarize the production, metabolism and physiological functions of H_2S, and explore its emerging pathogenic significance and therapeutic potential in several major cardiovascular diseases including atherosclerosis, coronary heart disease (CHD), heart failure, hypertension, pulmonary arterial hypertension (PAH), and myocardial ischemia/reperfusion (I/R) injury.

2. Production and metabolism of H_2S

H_2S is produced endogenously from L-cysteine (Fig. 1) by three enzymes, namely cystathionine-ß-synthase (CBS), cystathionine-γ-lyase (CSE) and the tandem enzymes cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3-MST). CSE and CBS are cytosolic enzymes with tissue-specific distributions. CBS is predominantly located in the central nervous system, whereas CSE predominates in the cardiovascular system, especially the myocardium and vascular smooth muscle cells (VSMCs) [4]. CAT and 3-MST are both cytosolic and mitochondrial enzymes, but the majority of these two enzymes exist in the mitochondria [5]. They are expressed in the brain and vascular endothelium [6,7]. CBS-driven H_2S production involves the condensation of homocysteine with L-cysteine to generate cystathionine. In the reactive process, H_2S is liberated [8]. CSE catalyzes the conversion of L-cysteine to pyruvate, thiocysteine and ammonia. Then, thiocysteine is decomposed nonenzymatically to form cysteine and H_2S [9]. CAT catalyzes the reaction between L-cysteine and α-ketoglutarate, leading to the synthesis of 3-mercaptopyruvate and L-glutamate. 3-MST transfers sulfur from 3-mercaptopyruvate into sulfurous acid, pyruvate and thiosulfate. Subsequently, thiosulfate is reduced to H_2S and glutathione disulfide in the presence of reduced glutathione [10]. The enzymatic mechanisms of H_2S production are shown in Fig. 2. After release, four fifths of H_2S exists as HS^- and a trace amount of S^{2-}, but only one fifth exists as undissociated H_2S under physiological conditions. Excess H_2S can be stored in two different forms: sulfane sulfur and acid-labile sulfur.

In order to maintain a proper physiological balance of its metabolism, H_2S can be eliminated through three routes (Fig. 3). Firstly, mitochondrial oxidative modification converts H_2S into thiosulfate, followed by further conversion into sulfite and finally into sulfate, the major end product of H_2S metabolism [11]. Because oxidation of cysteine can also increase urinary sulfate content, urinary thiosulfate acts as a specific marker for whole body H_2S synthesis. The second metabolic pathway is cytosolic methylation to dimethylsulfide via thiol S-methyltransferase. Lastly, binding of H_2S to hemoglobin leads to sulfhemoglobin formation [12]. These biosynthetic and degradative pathways for H_2S have been determined only recently, which will likely

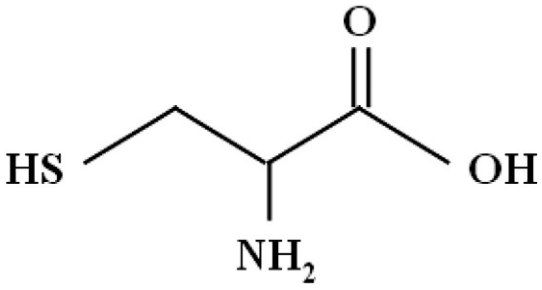

Fig. 1. The chemical structure of L-cysteine.

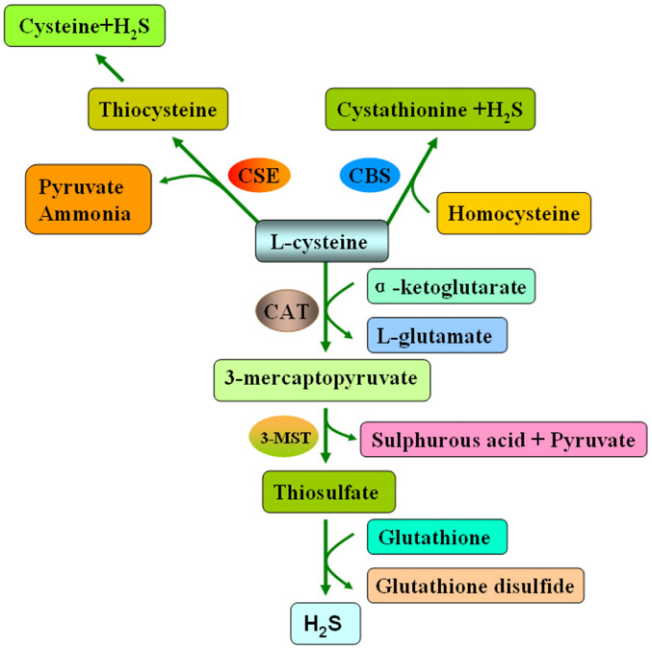

Fig. 2. Biosynthesis pathways of endogenous H_2S. The substrate for the production of endogenous H_2S is L-cysteine. CBS-driven H_2S generation is associated with the condensation of homocysteine with L-cysteine to yield cystathionine and H_2S. CSE catalyzes the transformation of L-cysteine to pyruvate, ammonia, and thiocysteine. The latter is then degraded to cysteine and H_2S. CAT stimulates the release of 3-mercaptopyruvate and L-glutamate via driving the reaction of L-cysteine and α-ketoglutarate. 3-Mercaptopyruvate is then catalyzed to sulfurous acid, pyruvate and thiosulfate by 3-MST. With the assistance from reduced glutathione, thiosulfate is reduced to H_2S and glutathione disulfide.