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Mini Review

Redox biology of hydrogen sulfide: Implications for physiology, pathophysiology, and pharmacology

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ABSTRACT

Hydrogen sulfide (H_2S) has emerged as a critical mediator of multiple physiological processes in mammalian systems. The pathways involved in the production, consumption, and mechanism of action of H_2S appear to be sensitive to alterations in the cellular redox state and O_2 tension. Indeed, the catabolism of H_2S through a putative oxidation pathway, the sulfide quinone oxido-reductase system, is highly dependent on O_2 tension. Dysregulation of H_2S homeostasis has also been implicated in numerous pathological conditions and diseases. In this review, the chemistry and the main physiological actions of H_2S are presented. Some examples highlighting the cytoprotective actions of H_2S within the context of cardiovascular disease are also reported. Elucidation of the redox biology of H_2S will enable the development of new pharmacological agents based on this intriguing new redox cellular signal.

Contents

Abbreviations: ARE, Antioxidant response element; CO, Carbon monoxide; CBS, Cystathionine-β-synthase; CGL, Cystathionine-γ-lyase; CcO, Cytochrome c oxidase; GSH, Glutathione; HSP, Heat shock protein; H_2S, Hydrogen sulfide; HIF, Hypoxic inducible factor; IL-1β, Interleukin 1 beta; IL-6, Interleukin 6; 3-MST, 3-mercaptopyruvate S-transferase; NO, Nitric oxide; NF-κB, Nuclear factor light chain enhancer of activated B cells; oxLDL, Oxidized low density lipoprotein; PAG, Propargylglycine; PGE2, Prostaglandin E2; NaHS, Sodium hydrosulfide; Na_2S, Sodium sulfide; SQR, Sulfide quinone oxido-reductase; TNF-α, Tumor necrosis factor alpha; VEGF, Vascular endothelial growth factor; VSMC, Vascular smooth muscle cells

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1. Introduction

Hydrogen sulfide (H_2S); a toxic gas, is endogenously produced, bioactive, and contributes to numerous physiological functions in mammalian systems. Studies support the possibility that H_2S has therapeutic potential for treating multiple diseases including cardiovascular diseases. For example, experimental animal studies show that H_2S may be effective in treating atherosclerosis and protecting against ischemia-reperfusion injury [1–3]. Interest in the cytoprotective actions of H_2S has grown since the discovery that it can induce a hypometabolic state characterized by decreased O_2 consumption, heart rate, and body temperature in non-hibernating rodents [4]. Although not discussed in this review, H_2S-dependent hypometabolism is an O_2-dependent phenomenon [5]. The proposed mitochondrial and signaling actions of H_2S make this molecule an attractive intervention for preventing and treating diseases and trauma-associated injuries. In this review article, we provide an overview of H_2S redox biology as it relates to the biological and pharmacological actions of this interesting new signaling molecule in mammalian systems.

2. Historical benefits of H_2S

The ancient Greeks, Egyptians, and Romans regularly bathed in natural sulfur springs as treatments for disease [6]. Depending on the microbiota and oxygen content, sulfur springs typically contain H_2S concentrations ranging from 1 to 500 μM [7] with anti-inflammatory, anti-bacterial, vasodilatory, and anti-fungal properties attributed to the sulfur-containing water [8]. Epidemiological studies report that a diet rich in organosulfur species is associated with longevity and decreased morbidity [9]. Members of the *Allium* genus (garlic and onions), which contain organosulfur compounds have a well-documented history of health benefits [10]. Indeed, garlic-derived compounds such as diallyl trisulfide release H_2S in the presence of cellular reductants like glutathione (GSH) [11]. Populations that consume garlic regularly have low blood pressure, low cholesterol, and less vascular disease [12]. While administration of exogenous sulfur-containing compounds shows strong promise as therapies, H_2S is also endogenously produced in many different human tissues.

3. Endogenous production of H_2S

In the early 1990s, it was discovered that H_2S is enzymatically produced by two cytosolic enzymes; cystathionine β-synthase (CBS) and cystathionine γ-lyase (CGL) [13,14]. Seminal work of Abe and Kimura showed, for the first time, that H_2S enhances long-term potentiation in the hippocampus [15]. Specifically, they demonstrated that H_2S was produced by CBS and that exogenous H_2S enhanced NMDA receptor-mediated responses. Since then many studies have shown that CBS and CGL are expressed in human tissues with H_2S contributing to physiological and pathophysiological processes (Table 1). In addition to CBS and CGL, there are other enzymes that produce H_2S with several utilizing cysteine as a substrate. The enzyme 3-mercaptopyruvate S-transferase (3-MST) is found in mitochondria and cytosol and produces H2S [16]. Several H2S producing enzymes are pyridoxal-5′-phosphate (PLP) dependent enzymes [17]. Moreover, other sulfur-containing amino acids, such as cystine and homocysteine, can be metabolized to generate H_2S. The enzymatic mechanisms of H_2S production are shown in Fig. 1. Many of these enzymes participate in the cellular sulfur cycle and have multiple enzymatic activities, including H_2S generation. Because the concentration of reduced sulfur species has an effect on many cellular processes [18], the activity of these enzymes is tightly regulated. Much of this regulation is linked to substrate availability [19]. Moreover, these are redox-sensitive enzymes, which exhibit increased activity under oxidative conditions [20]. Considering that H_2S; a reductant, is a product of these enzymes, it is conceivable that enzymatic activity may also be subject to negative feedback regulation. Finally, work by Wang et al. suggests that under certain conditions, such as oxidative stress, H_2S-producing enzymes translocate from the cytosol to mitochondria [21]. This dynamic regulation bolsters the argument that H_2S may function as a redox signaling molecule.

4. Catabolism of H_2S

Several regulated and unregulated non-enzymatic processes participate in H_2S catabolism. These pathways maintain *in vivo* H_2S concentrations, most likely, in the nM to low μM range. H_2S can react with heme proteins in mitochondria and therefore H_2S can function as a mitochondrial respiratory toxicant [22,23]. Fatal industrial accidents have been documented in individuals exposed to high concentrations of H_2S gas (e.g., >1000 pm) [24]. Therefore, the toxicological profile of H_2S has been well-studied and documented [24]. The mechanism of toxicity is through the binding of H_2S to cytochrome *c* oxidase (CcO) mediating respiratory inhibition [22]. However, this interaction is complex and poorly understood because H_2S can act as both an inhibitor and an electron donor for CcO [25]. H_2S binds to the oxidized states of the heme a-a_3 binuclear center, resulting in the reduction of the heme molecules [26]. Excess H_2S can also reduce Cu_B [27]. While the stoichiometry may vary, Cooper and Brown reported that 3 molecules of H_2S bind per inhibited CcO [28]. In this inhibitory reaction, H_2S is oxidized to sulfane sulfur and this is coupled to consumption of molecular O_2 [28]. Unlike nitric oxide ($^{\bullet}NO$), the inhibition of CcO by H_2S is noncompetitive with O_2 [27,29]. In addition, H_2S can also directly reduce the electron carrier cytochrome *c* producing the one electron oxidation product, the thiyl radical ($^{\bullet}SH$) [28].

Rhodanese, a mitochondrial sulfur transferase enzyme, catalyzes the oxidation of H_2S [30]. It is one part of three enzymatic activities characterized as a major pathway for H_2S catabolism. This pathway consists of a sulfide quinone oxido-reductase (SQR), a sulfur dioxygenase, and the sulfur transferase enzyme rhodanese (Figs. 2 and 3). H_2S reduces the external disulfide on the SQR to form a thiol (RSH) and a perthiol (RSSH). This two electron oxidation of H_2S reduces the FAD prosthetic group, which uses ubiquinone (Q) as an electron acceptor [31] The second sulfur

Table 1
Biological and therapeutic actions of H_2S are O_2-dependent.

Biological context	Low O_2	High O_2
Inflammation	Anti-inflammatory: IL-10; ↓ IL-6, ICAM	Pro-inflammatory: ↑ NF-κB, TNF-α
Vasoactivity	Vasodilatory: ↑ K_{ATP} channel conductance	Vasoconstrictive
Angiogenesis	Pro-angiogenic: VEGF, Hif1-α	No effect
Respiratory inhibition	Higher [H_2S] results in more inhibition	O_2 acts as an H_2S antagonist: ↑SOx
Ischemia-reperfusion	Ischemic tissue has higher [H_2S]: mito K_{ATP}, ARE genes	Unknown