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Invited critical review

Hydrogen sulfide in signaling pathways

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ABSTRACT

For a long time hydrogen sulfide (H_2S) was considered a toxic compound, but recently H_2S (at low concentrations) has been found to play an important function in physiological processes. Hydrogen sulfide, like other well-known compounds — nitric oxide (NO•) and carbon monoxide (CO) is a gaseous intracellular signal transducer. It regulates the cell cycle, apoptosis and the oxidative stress. Moreover, its functions include neuromodulation, regulation of cardiovascular system and inflammation. In this review, I focus on the metabolism of hydrogen sulfide (including enzymatic pathways of H_2S synthesis from L- and D-cysteine) and its signaling pathways in the cardiovascular system and the nervous system. I also describe how hydrogen sulfide may be used as therapeutic agent, i.e. in the cardiovascular diseases.

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Contents

1. Introduction

Hydrogen sulfide (H_2S), like other molecules (nitric oxide (NO•); various isoforms of NO• synthase catalyze NO• production [1], and carbon monoxide (CO) — a product of heme metabolism [1]) is the inorganic gas, referred to as a gasotransmitter. Gasotransmitters are endogenously generated gaseous signaling molecules [1–3]. Their production does not rely on complicated chemical processes or on supplies from multiple substrates. The simplicity of gasotransmitters allows them to travel intracellularly and intercellularly quickly and on short notice [1]. They are present on all organs, cells, and different intracellular organelles in significant abundance [1]. The pathways of H_2S, CO and NO• biosynthesis interact with each other, i.e. they have positive or negative impact on the concentration and properties of the other. However, there are differences between these gasotransmitters, i.e. half lives (hydrogen sulfide, like NO• is short lived and acts only close to sites of biosynthesis) [4–7].

H_2S is a mediator of many physiological and/or pathological processes. Some of these effects are ascribed to the formation of protein persulfides, or protein S-sulfhydration, i.e. conversion of cysteine residues –SH to persulfides –S–SH [8]. H_2S plays an important role in regulating the nervous system and the cardiovascular system. It regulates apoptosis, the cell cycle and the oxidative stress. H_2S has cardioprotective action, neuromodulation properties and may modulate inflammation process, gastrointestinal function, mitochondrial function

Abbreviations: CAT, cysteine aminotransferase; CBS, cystathionine β-synthase; CO, carbon monoxide; CSE, cystathionine γ-lyase; DAO, D-amino acid oxidase; ERK, extracellular signal-regulated kinase; eNOS, endothelial nitric oxide synthase; GSH, reduced form of glutathione; H_2O_2, hydrogen peroxide; HOCl, hypochlorous acid; HS^-, hydrosulfide anion; H_2S, hydrogen sulfide; MAPK, mitogen activated protein kinase; MST, 3-mercaptopyruvate sulfurtransferase; NaHS, sodium hydrosulfide; Na_2S, sodium sulfide; NMDA, N-methyl-D-aspartic; NO•, nitric oxide; O_2^-•, superoxide anion; $ONOO^-$, peroxynitrite; PKA, protein kinase A; RNS, reactive nitrogen species; ROS, reactive oxygen species; SO_2, sulfur dioxide; $S_2O_3^{2-}$, thiosulfate; SO_4^{2-}, sulfate; VSMC, vascular smooth muscle cell.

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and energy metabolism [9]. Hundreds of papers and books with the keywords: "hydrogen sulfide" and "H_2S" have been published [1,10]. Numerous papers have demonstrated different roles of H_2S in signaling pathways in a range of organisms, including both animals and plants [1,2,11–19].

Plasma concentration of H_2S is in 34–65 μM range [20], but in the brain the physiological concentration of H_2S is up to threefold higher than in serum [21,22]. Results of Olson [23] showed that H_2S concentrations are between 30 and 300 μM in plasma or blood. The level of H_2S in various human tissues may depend on the donor's age and the method, which is used for measurement [18,24]. Endogenous level of H_2S is modulated by different metabolic pathways, including H_2S oxidation [25–27], which occurs in the mitochondria [9]. The oxidation products include persulfide, sulfite, thiosulfate ($S_2O_3^{2-}$) and sulfate (SO_4^{2-}) [9]. The gas/water coefficient of distribution for hydrogen sulfide is 0.39, and physiological pH about 20% (at 37 °C) of the total free sulfide is present as dissolved gas (Fig. 1) [28–30]. At high concentration or, administered in the short time, hydrogen sulfide becomes toxic via inhibition of mitochondrial cytochrome c oxidase and mitochondrial respiration [31].

Wedmann et al. [32] demonstrated that when working with H_2S, the final experiment outcome depends on the source of hydrogen sulfide and used methods. There are different ways to donate H_2S to cells. Common compounds such as sodium hydrosulfide (NaHS) and sodium sulfide (Na_2S) have been used extensively to give a short burst of hydrogen sulfide, i.e. NaHS dissociated to Na^+ and HS^-, and then partially binding to H^+ to form un-dissociated hydrogen sulfide [33]. GYY4137, AP97 and AP105 are donors, which release H_2S in a more physiological manner, and can be targeted to organelles [13,14,34]. The purpose of this work is the characteristics of the signal pathways of hydrogen sulfide.

2. Biogenesis and metabolic pathways of hydrogen sulfide in vivo and in vitro

In mammalian cells, endogenous H_2S is synthesized by four enzymes: cystathionine γ-lyase (CSE, EC 4.4.1.1), cystathionine β-synthase (CBS, EC 4.2.1.22), cysteine aminotransferase (CAT, EC 2.6.1.3) and 3-mercaptopyruvate sulfurtransferase (MST, EC 2.8.1.2). These enzymes are involved in the transsulfuration and reverse transsulfuration pathways as described earlier [10,18,34–37]. CBS (the main H_2S-producing enzyme in the central nervous system) and CSE (presents in the vasculature, liver and kidney) are the enzymes using amino acids: L-cysteine (which is synthesized from L-methionine through the transsulfuration), L-homocysteine and L-cystathionine to produce hydrogen sulfide with pyridoxal 5′ phosphate (vitamin B_6) as a cofactor [10,37–42]. The level of CBS is low in the embryonic brain, but it significantly increases from the late prenatal to the early postnatal period and then declines in the adult brains [43,44]. CBS expression is associated with the generation and differentiation of the lineage in brain development [43,44]. Its expression is up-regulated in reactive astrocytes [44].

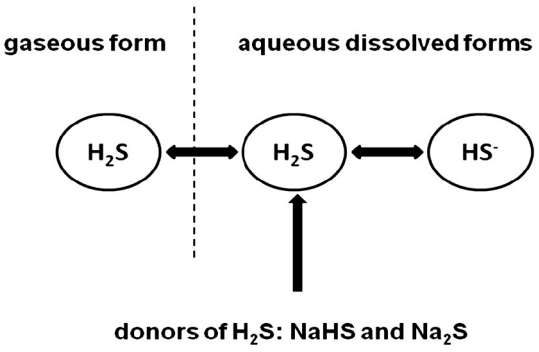

Fig. 1. Different forms of hydrogen sulfide in aqueous (H_2S and hydrosulfide anion (HS^-)) and gaseous phase (H_2S) [30,131; modified].

Recent different results have reported that H_2S production can use also D-cysteine [17,45]. D-Cysteine is metabolized by D-amino acid oxidase (DAO) to an achiral 3-mercaptopyruvate, which is also produced by CAT from L-cysteine in the presence of α-ketoglutarate [17]. Fig. 2 demonstrates the known enzymatic pathways of endogenous H_2S biosynthesis from L-cysteine and D-cysteine. There are two possible sources of D-cysteine: racemase-induced hiral change of L-cysteine and absorption from food. Cysteine is structurally similar to serine with an OH replaced by an SH. Aspartate racemase is homologous to CAT, which has an affinity for both aspartate and cysteine [45,46]. It is possible that serine racemase or aspartate racemase changes L-cysteine to D-cysteine [45]. D-Cysteine-dependent pathway operates predominantly in the brain (especially in the cerebellum) and the kidney [17,45]. Moreover, the production of H_2S from D-cysteine is higher in the cerebellum than in other regions of the brain; but the production of hydrogen sulfide in the kidney is 7 times greater than in the cerebellum. The generation of H_2S from D-cysteine is 80 times greater than from L-cysteine in the kidney [17,45].

D-Cysteine may have therapeutic potential. Moreover, it is less toxic than L-cysteine [17]. Administration of D-cysteine protects primary cultures of cerebellar neurons from the oxidative stress by hydrogen peroxide (H_2O_2) and attenuates ischemia–reperfusion injury in the kidney more than L-cysteine [45].

Recently, Kimura [17] has demonstrated that the production of H_2S by CSE and the 3MST/CAT pathway may be regulated by Ca^{2+}. In the steady state, low intracellular concentrations of Ca^{2+}, CSE and 3MST/CAT pathway produce H_2S. When cells are stimulated and the intracellular level of Ca^{2+} is increased by Ca^{2+} influx and/or Ca^{2+} release from the intracellular stores, the generation of hydrogen sulfide by CSE is decreased by approximately 50% and that via 3MST/CAT pathway is stopped [17].

3. Hydrogen sulfide as a signaling molecule

Hydrogen sulfide as a signaling molecule is involved in cell signal transduction in the nervous system, the circulatory system, as well as in many organs [47–58]. H_2S exerts powerful effects on smooth muscle cells, inflammatory cells, endothelial cells, nuclear transcription factors, endoplasmic reticulum and mitochondria [59–61]. Hong et al. [62] demonstrated that H_2S promotes proliferation and migration of human colon cancer SW 480 cells in vitro; and the mechanisms of its action may involve up-regulation of SIRT1 expression. In colorectal and ovarian cancers, an increase in the intratumor synthesis of H_2S by CBS plays an important function in promoting the cellular bioenergetics, proliferation and migration of cancer cells [63]. H_2S upregulates *Porphyromonas gingivalis* lipopolysaccharide-induced expression of Il-6 and Il-8 in periodontal fibroblast via activation of nuclear factor-kappa B signaling, which may promote the development of periodontitis [64].

3.1. H_2S as a gasotransmitter in cardiovascular system

Preclinical experiments concerning cardiovascular illnesses have shown that the administration of physiological or pharmacological concentrations of H_2S protects blood vessels, attenuates myocardial injury, regulates blood pressure and limits inflammation [61]. H_2S showing activity in the circulatory system causes dilation of blood vessels, because H_2S functions as an endothelial-derived hyperpolarizing factor (EDHF) and its vasorelaxant activity is ascribed to activation of K_{ATP} channels [9]. K_{ATP} channels are widely distributed in mitochondrial and plasma membranes [9]. K_{ATP}-sensitive potassium channels are found in many structures, i.e. in smooth muscle cells of blood vessels. H_2S through impact on the K_{ATP} channels affect contractility of smooth muscle of the blood, regulating blood pressure. Opening the channels K_{ATP} protects against excessive contraction of smooth muscle cells and lowers

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