Hydrogen Sulfide and Polysulfide Signaling

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Contributor: Hideo Kimura

We discovered H2S as a signaling molecule which is produced by enzymes to modulate the synaptic transmission and relax vasculature. The cytoprotective effect, anti-inflammatory activity, energy formation, and oxygen sensing by H2S have been subsequently demonstrated. Two additional pathways for the production of H2S with 3-mercaptopyruvate sulfurtransferase (3MST) from l- and d-cysteine have been identified. We also discovered that hydrogen polysulfides (H2Sn, n ≥ 2) are potential signaling molecules produced by 3MST. H2Sn regulate the activity of ion channels and enzymes, as well as even the growth of tumors. S-Sulfuration (S-sulfhydration) proposed by Snyder is the main mechanism for H2S/H2Sn underlying regulation of the activity of target proteins.

hydrogen sulfide polysulfides S-sulfuration nitric oxide hydrogen peroxide S-nitrosylation S-sulfenylation 3MST

1. Identification of H_2S as a Signaling Molecule

Patients that recover from H_2S poisoning show cognitive decline, and the levels of neurontransmitters in the brains of animals exposed to H_2S change, suggesting that the brain is vulnerable to H_2S toxicity [1]. Warenycia et al. measured the levels of H_2S accumulated in the brain of rats exposed to H_2S when they discovered a certain amount of H_2S in the brain even without exposure to H_2S [2]. Although the concentrations were overestimated, the existence of endogenous H_2S was identified in the brain.

Pyridoxal 5′-phosphate-dependent enzymes, cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE), have been suggested to regulate several pathways. CBS catalyzes the first step of the transsulfuration pathway in which cystathionine is produced from serine and homocysteine, and cystathionine is further catalyzed by CSE to cysteine. An alternate pathway exists in which CBS catalyzes the condensation of cysteine with homocysteine to generate cystathionine and H_2S [3][4]. CSE catalyzes an elimination reaction which metabolizes cysteine to pyruvate, NH_3, and H_2S [3][4]. However, rather than being recognized as a physiologically active molecule, in these early studies, H_2S was merely thought to be a byproduct of the metabolic pathways.

The observations that H_2S is produced by enzymes and exists in the brain prompted us to study a physiological role of this molecule. The activities of CBS and CSE have been intensively studied in the liver and kidney, but little is known about them in the brain. We found CBS in the brain and confirmed the production of H_2S, which is augmented by *S*-adenosyl methionine (SAM) [5].

Other gaseous signaling molecules NO and carbon monoxide (CO) induce hippocampal long-term potentiation (LTP), a synaptic model of memory formation, as retrograde messengers, which are produced at postsynapse and released to presynapse to facilitate a release of a neurotransmitter glutamate from presynapse [6][7][8][9][10]. We examined whether or not H_2S has a similar effect. H_2S facilitated the induction of LTP by enhancing the activity of *N*-methyl-d-aspartate (NMDA) receptors but not as a retrograde messenger [5].

NMDA receptors are activated by a reducing substance dithiothreitol (DTT) through the reduction of a cysteine disulfide bond located at the hinge of the ligand-binding domain [11]. Because H_2S is a reducing substance, it is likely to be a mechanism for facilitating the induction of LTP. However, H_2S with one-tenth of the concentration of DTT exerted a greater effect than that of DTT [5]. This observation suggested that there is an additional mechanism for LTP induction by H_2S. The prominent neuroscientist Solomon Snyder commented the following in *Science News*: “They have very impressive evidence that H_2S is a potential neurotransmitter. It is an exciting paper that should stimulate a lot of people’s interest” [12].

2. Identification of H_2S_n as Signaling Molecules

During this study, we found that a batch of NaHS, i.e., the sodium salt of H_2S, with yellowish color was much more potent than the colorless batch. We successfully reproduced a solution with a similar color by dissolving elemental sulfur into Na_2S solution according to a report by Searcy and Lee [13]. The color came from H_2S_n, which induces Ca^{2+} influx in astrocytes much more potently than H_2S [14][15][16]. H_2S_n are natural inorganic polymeric sulfur–sulfur species or sulfane sulfur, which we later found to be produced by 3-mercaptopyruvate sulfurtransferase (3MST) from 3-mercaptopyruvate [17][18][19] and the partial oxidation of H_2S [16], such as via the chemical interaction with NO [20][21]. H_2S_2 (2.6 μM) exists in the brain almost equivalent to the level of H_2S (3 μM) [22]. Ca^{2+} influx induced in astrocytes by AITC, cinnamaldehyde, selective activators of TRPA1 channels, and Na_2S_3 was greatly suppressed by HC030031 and AP-18, selective inhibitors of TRPA1 channels. In astrocytes transfected with TRPA1-siRNA, Ca^{2+} influx was not efficiently induced by Na_2S_3 [16]. The EC_{50} value for H_2S was 116 μM, while that for H_2S_3 was 91 nM, suggesting that H_2S_n rather than H_2S are ligands for TRPA1 channels [23][14][15][16]. The amino terminus of TRPA1 channels has 24 cysteine residues [24], and two cysteine residues Cys422 and Cys634 are sensitive to H_2S_n [25].

S-Sulfuration (*S*-sulfuhydration) was proposed by Snyder and colleagues to regulate the activity of target proteins by H_2S [26]. This proposal needs a minor revision to highlight H_2S_n but not H_2S *S*-sulfurate cysteine residues. In contrast, H_2S *S*-sulfurates oxidized cysteine residues such as those *S*-nitrosylated and *S*-sulfenylated [27]. H_2S_n *S*-sulfurate (*S*-sulfhydrate) two cysteine residues of TRPA1 channels to induce the conformational changes to activate the channels. As an alternative mechanism, one cysteine residue, which is *S*-sulfurated, reacts with the remaining cysteine residue to generate a cysteine disulfide bond. Although the conformation has not been examined in detail, the latter mechanism may induce conformational changes more efficiently than the former one.

3. Synergy and Crosstalk between H_2S and NO

H_2S relaxes vascular smooth muscle in synergy with NO [28]. A similar result was also obtained in the ileum [29]. Whiteman et al. proposed that the chemical interaction of H_2S with NO generate nitrosothiol, which releases NO in the presence of Cu^{2+} [30]. Filipovic et al. reported that H_2S and NO produces nitroxyl (HNO) as a major product, as well as H_2S_n [31][32], while Cortese-Krott et al. suggested that $SSNO^-$ as a major product with H_2S_n as a minor one [33]. We proposed that H_2S_n are major products [20]. The effect of H_2S_n and that of the products obtained from the mixture of Na_2S and diethylamine NONOate, an NO donor, were eliminated when they were exposed to cyanide or DTT [20]. In contrast, HNO is resistant to cyanide, and $SSNO^-$ is resistant to DTT. Based on these observations, H_2S_n are potential chemical entities produced from H_2S and NO [20][32][33]. Bogdandi et al. recently suggested that H_2S_n transiently activate TRPA1 channels at the early phase of the production from H_2S and NO, while the more stable product $SSNO^-$ sustainably activates the channels [34].

4. Vascular Tone Regulation by H_2S and H_2S_n

Since H_2S relaxes vascular smooth muscle in synergy with NO [28] and activates ATP-dependent K^+ (K_{ATP}) channels [35], it has been suggested that H_2S is a potential endothelial-derived hyperpolarizing factor (EDHF), which is a component of endothelial-derived relaxing factor (EDRF) [36]. However, previous studies showed that the hyperpolarization induced by EDHF is resistant to glibenclamide, a K_{ATP} channel blocker [37][38]. The relaxation of vascular smooth muscle in the mesenteric bed, which is mediated predominantly by EDHF, is rather abolished by apamine, a blocker of Ca^{2+}-activated K^+ channels [39].

H_2S_n are potential EDHFs (Figure 1). H_2S_n produced by 3MST together with cysteine aminotransferase (CAT), both of which are localized to the vascular endothelium [17][40][41], or H_2S_n generated by the chemical interaction between H_2S and NO produced by endothelial NO synthase (eNOS) can activate TRPA1 channels [16][20] localized to myoendothelial junctions. The channels induce Ca^{2+} influx, which activate Ca^{2+}-activated K^+ channels to hyperpolarize the endothelial cell plasma membrane. The change in membrane potential is conducted via myoendothelial gap junctions to hyperpolarize the vascular smooth muscle [42].

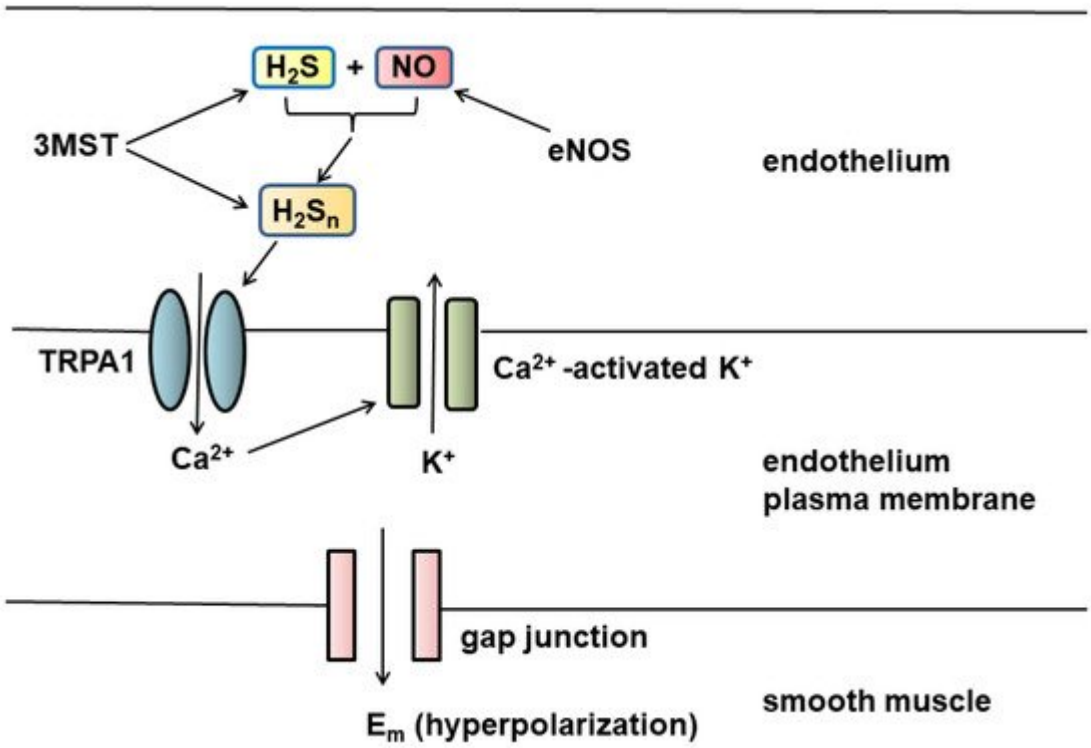

Figure 1. H_2S_n are potential EDHFs. Both 3MST and eNOS are localized to endothelium. H_2S_n produced by 3MST or by the chemical interaction between H_2S and NO activate TRPA1 channels present in myoendothelial junctions to induce Ca^{2+} influx, which activates Ca^{2+}-dependent K^+ channels. The change in membrane potential is conducted via gap junction to hyperpolarize the smooth muscle plasma membrane.

5. Cytoprotective Effect of H_2S, H_2S_n, and H_2SO_3

The impression of H_2S as toxic gas led to its cytoprotective effect being overlooked [43]. Expecting that all cells would be killed by H_2S, I applied NaHS to cells and incubated for overnight. On the contrary, cells were lively and survived from the toxin. H_2S increases the production of glutathione (GSH), a major intracellular antioxidant, by enhancing the activity of cystine/glutamate antiporter, which incorporates cystine into cells, and of glutamate cysteine ligase (GCL), a rate-limiting enzyme for GSH production [43][44]. H_2S also facilitates the translocation of GSH into mitochondria [44]. The protective activity of H_2S is also exerted through the stabilization of membrane potential by enhancing the activity of K_{ATP} channels and cystic fibrosys transmembrane conductance regulator (CFTR) Cl^- channels [45]. Lefer and colleagues demonstrated that H_2S protects the heart from ischemia/reperfusion injury by preserving mitochondrial function [46].

6. Signaling by H_2S, H_2S_n through *S*-Sulfuration and Bound Sulfane Sulfur

In addition to CBS and CSE, 3MST, along with CAT or DAO, was recognized to produce H_2S from l- or d-cysteine, respectively [41][47][48]. Subsequently, 3MST was found to produce H_2S_n and other *S*-sulfurated molecules such as cysteine persulfide, GSSH, and *S*-sulfurated cysteine residues [17][18][49]. Other enzymes such as sulfide-quinone

oxidoreductase (SQR), haemoglobin, neuroglobin, catalase, super oxide dismutase (SOD), cysteine tRNA synthetase (CARS), and peroxidases have been identified to produce H_2S_n and other *S*-sulfurated molecules [50][51][52][53][54][55][56][57][58].

In total, 10–20% of cysteine residues of proteins are *S*-sulfurated [26], also observed as a part of bound sulfane sulfur, which releases H_2S under reducing conditions, including H_2S_n, cysteine persulfide, GSSH, and *S*-sulfurated cysteine residues [59][60][61][62]. In cells and tissues, 5–12% of total protein cysteine residues are oxidized, such as *S*-nitrosylated (P-CysSNO) and *S*-sulfenylated (P-CysSOH), and this can be increased to more than 40% under oxidative conditions [63] (Figure 2). The amount of bound sulfane sulfur and its associated species is distinct among tissues. For example, heart homogenates release H_2S under reducing conditions much less than those from the liver and the brain, while heart homogenates absorb H_2S as fast as liver homogenates [62]. P-CysSNO and P-CysSOH react with H_2S to generate P-CysSSH, while they do not release H_2S under reducing conditions. These observations suggest that the heart may contain P-CysSNO and P-CysSOH more abundantly than the liver and the brain.

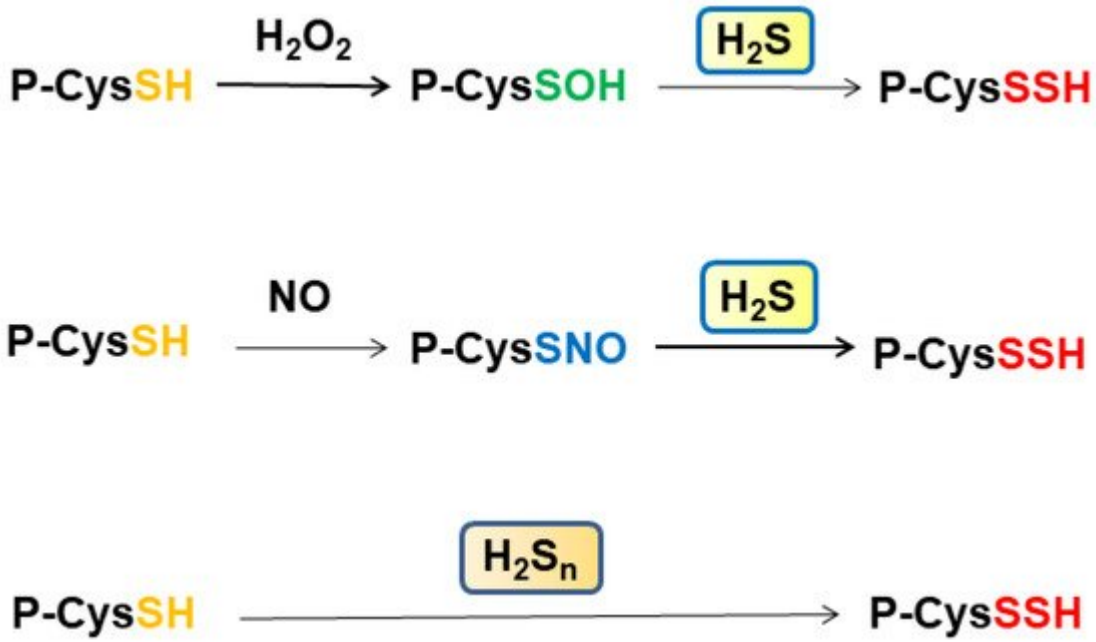

Figure 2. *S*-Sulfuration of cysteine residues by H_2S and H_2S_n. Cysteine residues are *S*-sulfenylated by H_2O_2 and *S*-nitrosylated by NO. These oxidized cysteine residues are *S*-sulfurated by H_2S. In contrast, cysteine residues are *S*-sulfurated by H_2S_n.

Some cysteine residues are oxidized by H_2O_2 to generate S-nitrosylated cysteine residues, and some others are S-nitrosylated by NO. These oxidized cysteine residues are S-sulfurated by H_2S rather than H_2S_n (Figure 2). Cys150 and Cys156 of GAPDH may be in the different oxidation state as described previously [26][64]. Zivanovic et al. demonstrated that the activity of manganese superoxide dismutase is suppressed through S-sulfenylation by H_2O_2, while the activity is recovered by H_2S, which S-sulfurates the S-sulfenylated cysteine residues [65]. The same group showed that epidermal growth factor (EGF) activates its receptor in which the levels of S-sulfenylated

cysteine residues are increased at the early phase, and those of S-sulfurated residues are increased at late phase when the expression of H_2S producing enzymes is enhanced. H_2S S-sulfurates those S-sulfenylated cysteine residues to regulate their activity (Figure 2).

Another role of S-sulfuration is that it enables proteins to recover their functions from over-oxidization. Sulfinic (Protein-$CysSO_2H$) and sulfonic acids (Protein-$CysSO_3H$) are not reduced back to Protein-CysSH by thioredoxin and deteriorate the protein function. In contrast, S-sulfurated proteins P-$CysSSO_2H$ and P-$CysSSO_3H$ can be reduced by thioredoxin to P-CysSH [65][66].

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