# Hydrogen Sulfide and Polysulfide Signaling

Subjects: Biochemistry & Molecular Biology 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 I- and d-cysteine have been identified. We also discovered that hydrogen polysulfides (H2Sn,  $n \ge 2$ ) 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.

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

# **1.** Identification of H<sub>2</sub>S 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 <sup>[1]</sup>. 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  $H_2S$  <sup>[2]</sup>. Although the concentrations were overestimated, the existence of endogenous  $H_2S$  was identified in the brain.

Pyridoxal 5'-phosphate-dependent enzymes, cystathionine  $\beta$ -synthase (CBS) and cystathionine  $\gamma$ -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<sub>2</sub>S <sup>[3][4]</sup>. CSE catalyzes an elimination reaction which metabolizes cysteine to pyruvate, NH<sub>3</sub>, and H<sub>2</sub>S <sup>[3][4]</sup>. However, rather than being recognized as a physiologically active molecule, in these early studies, H<sub>2</sub>S 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) <sup>[5]</sup>.

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  $[\Omega][\mathcal{I}][\mathcal{B}][\mathcal{D}][\mathcal{I}][\mathcal{D}]$ . We examined whether or not H<sub>2</sub>S has a similar effect. H<sub>2</sub>S facilitated the induction of LTP by enhancing the activity of *N*-methyl-d-aspartate (NMDA) receptors but not as a retrograde messenger <sup>[5]</sup>.

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 <sup>[11]</sup>. 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 <sup>[5]</sup>. 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" <sup>[12]</sup>.

### 2. Identification of H<sub>2</sub>S<sub>n</sub> as Signaling Molecules

During this study, we found that a batch of NaHS, i.e., the sodium salt of H<sub>2</sub>S, 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<sub>2</sub>S solution according to a report by Searcy and Lee <sup>[13]</sup>. The color came from H<sub>2</sub>S<sub>n</sub>, which induces Ca<sup>2+</sup> influx in astrocytes much more potently than H<sub>2</sub>S <sup>[14][15][16]</sup>. H<sub>2</sub>S<sub>n</sub> 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 <sup>[17]</sup> <sup>[18][19]</sup> and the partial oxidation of H<sub>2</sub>S <sup>[16]</sup>, such as via the chemical interaction with NO <sup>[20][21]</sup>. H<sub>2</sub>S<sub>2</sub> (2.6 µM) exists in the brain almost equivalent to the level of H<sub>2</sub>S (3 µM) <sup>[22]</sup>. Ca<sup>2+</sup> influx induced in astrocytes by AITC, cinnamaldehyde, selective activators of TRPA1 channels, and Na<sub>2</sub>S<sub>3</sub> was greatly suppressed by HC030031 and AP-18, selective inhibitors of TRPA1 channels. In astrocytes transfected with TRPA1-siRNA, Ca<sup>2+</sup> influx was not efficiently induced by Na<sub>2</sub>S<sub>3</sub> <sup>[16]</sup>. The EC<sub>50</sub> value for H<sub>2</sub>S was 116 µM, while that for H<sub>2</sub>S<sub>3</sub> was 91 nM, suggesting that H<sub>2</sub>S<sub>n</sub> rather than H<sub>2</sub>S are ligands for TRPA1 channels <sup>[23][14][15][16]</sup>. The amino terminus of TRPA1 channels has 24 cysteine residues <sup>[24]</sup>, and two cysteine residues Cys422 and Cys634 are sensitive to H<sub>2</sub>S<sub>n</sub> <sup>[25]</sup>.

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<sub>2</sub>S and NO

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

#### 4. Vascular Tone Regulation by $H_2S$ and $H_2S_n$

Since H<sub>2</sub>S relaxes vascular smooth muscle in synergy with NO <sup>[28]</sup> and activates ATP-dependent K<sup>+</sup> (K<sub>ATP</sub>) channels <sup>[35]</sup>, it has been suggested that H<sub>2</sub>S is a potential endothelial-derived hyperpolarizing factor (EDHF), which is a component of endothelial-derived relaxing factor (EDRF) <sup>[36]</sup>. However, previous studies showed that the hyperpolarization induced by EDHF is resistant to glibenclamide, a K<sub>ATP</sub> channel blocker <sup>[37][38]</sup>. 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<sup>2+</sup>-activated K<sup>+</sup> channels <sup>[39]</sup>.

 $H_2S_n$  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  $\frac{[17][40][41]}{1}$ , or  $H_2S_n$  generated by the chemical interaction between  $H_2S$  and NO produced by endothelial NO synthase (eNOS) can activate TRPA1 channels  $\frac{[16][20]}{10}$  localized to myoendothelial junctions. The channels induce  $Ca^{2+}$  influx, which activate  $Ca^{2+}$ -activated K<sup>+</sup> 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  $\frac{[42]}{10}$ .



**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<sub>2</sub>S, H<sub>2</sub>S<sub>n</sub>, and H<sub>2</sub>SO<sub>3</sub>

The impression of H<sub>2</sub>S as toxic gas led to its cytoprotective effect being overlooked <sup>[43]</sup>. Expecting that all cells would be killed by H<sub>2</sub>S, I applied NaHS to cells and incubated for overnight. On the contrary, cells were lively and survived from the toxin. H<sub>2</sub>S 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 <sup>[43][44]</sup>. H<sub>2</sub>S also facilitates the translocation of GSH into mitochondria <sup>[44]</sup>. The protective activity of H<sub>2</sub>S is also exerted through the stabilization of membrane potential by enhancing the activity of K<sub>ATP</sub> channels and cystic fibrosys transmembrane conductance regulator (CFTR) Cl<sup>-</sup> channels <sup>[45]</sup>. Lefer and colleagues demonstrated that H<sub>2</sub>S protects the heart from ischemia/reperfusion injury by preserving mitochondrial function <sup>[46]</sup>.

# 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 I- 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 <sup>[26]</sup>, 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 <sup>[59][60][61][62]</sup>. 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 <sup>[63]</sup> (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 <sup>[62]</sup>. 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 Snitrosylated by NO. These oxidized cysteine residues are S-sulfurated by  $H_2S$ . In contrast, cysteine residues are Ssulfurated by  $H_2S_n$ .

Some cysteine residues are oxidized by  $H_2O_2$  to generate S-nitrosylated cysteine residues, and some others are Snitrosylated 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 <sup>[26][64]</sup>. 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 <sup>[65]</sup>. 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<sub>2</sub>H) and sulfonic acids (Protein-CysSO<sub>3</sub>H) are not reduced back to Protein-CysSH by thioredoxin and deteriorate the protein function. In contrast, S-sulfurated proteins P-CysSSO<sub>2</sub>H and P-CysSSO<sub>3</sub>H can be reduced by thioredoxin to P-CysSH <sup>[65][66]</sup>.

#### References

- 1. Reiffenstein, R.J.; Hulbert, W.C.; Roth, S.H. Toxicology of hydrogen sulfide. Annu. Rev. Pharmacol. Toxic 1992, 32, 109–134.
- Warenycia, M.W.; Goodwin, L.R.; Benishin, C.G.; Reiffenstein, R.J.; Grancom, D.M.; Taylor, J.D.; Dieken, F.P. Acute hydrogen sulfide poisoning. Demonstration of selective uptake of sulfide by the brainstem by measurement of brain sulfide levels. Biochem. Pharmacol. 1989, 38, 973–981.
- 3. Stipanuk, M.H.; Beck, P.W. Characterization of the enzymic capacity for cysteine desulphhydration in liver and kidney of the rat. Biochem. J. 1982, 206, 267–277.
- Griffith, O.W. Mammalian Sulfur Amino Acid Metabolism: An Overview. In Methods in Enzymology; Academic Press: New York, NY, USA, 1987; Volume 143, pp. 366–376.
- 5. Abe, K.; Kimura, H. The possible role of hydrogen sulfide as an endogenous neuromodulator. J. Neurosci. 1996, 16, 1066–1071.
- O'Dell, T.J.; Hawkins, R.D.; Kandel, E.R.; Arancio, O. Tests of the roles of two diffusible substances in long-term potentiation: Evidence for nitric oxide as a possible early retrograde messenger. Proc. Natl. Acad. Sci. USA 1991, 88, 11285–11289.
- 7. Schuman, E.M.; Madison, D.V. A requirement for the intercellular messenger nitric oxide in long-term potentiation. Science 1991, 254, 1503–1506.
- 8. Haley, J.E.; Wilcox, G.L.; Chapman, P.F. The role of nitric oxide in hippocampal long-term potentiation. Neuron 1992, 8, 211–216.
- Stevens, C.F.; Wang, Y. Reversal of long-term potentiation by inhibitors of haem oxygenase. Nature 1993, 364, 147– 149.
- Zhuo, M.; Small, S.A.; Kandel, E.R.; Hawkins, R.D. Nitric oxide and carbon monoxide produce activity-dependent longterm synaptic enhancement in hippocampus. Science 1993, 260, 1946–1950.

- Aizenman, E.; Lipton, D.A.; Loring, R.H. Selective modulation of NMDA responses by reduction and oxidation. Neuron 1989, 2, 1257–1263.
- 12. Travis, J. The rotten smell of memory: It's a gas. Sci. News 1996, 149, 116.
- 13. Searcy, D.G.; Lee, S.H. Sulfur reduction by human erythrocytes. J. Exp. Zool. 1998, 282, 310–322.
- 14. Nagai, Y.; Tsugane, M.; Oka, J.-I.; Kimura, H. Polysulfides induce calcium waves in rat hippocampal astrocytes. J. Pharmacol. Sci. 2006, 100, 200.
- 15. Oosumi, K.; Tsugane, M.; Ishigami, M.; Nagai, Y.; Iwai, T.; Oka, J.-I.; Kimura, H. Polysulfide activates TRP channels and increases intracellular Ca2+ in astrocytes. Bull. Jpn. Soc. Neurochem. 2010, 49, 517.
- Kimura, Y.; Mikami, Y.; Osumi, K.; Tsugane, M.; Oka, J.; Kimura, H. Polysulfides are possible H2S-derived signaling molecules in rat brain. FASEB J. 2013, 27, 2451–2457.
- 17. Kimura, Y.; Toyofuku, Y.; Koike, S.; Shibuya, N.; Nagahara, N.; Lefer, D.; Ogasawara, Y.; Kimura, H. Identification of H2S3 and H2S produced by 3-mercaptopyruvate sulfurtransferase in the brain. Sci. Rep. 2015, 5, 14774.
- Kimura, Y.; Koike, S.; Shibuya, N.; Lefer, D.; Ogasawara, Y.; Kimura, H. 3-Mercaptopyruvate sulfurtransferase produces potential redox regularots cysteine- and glutathione-persulfide (Cys-SSH and GSSH) together with signaling molecules H2S2, H2S3 and H2S. Sci. Rep. 2017, 7, 10459.
- Nagahara, N.; Koike, S.; Nirasawa, T.; Kimura, H.; Ogasawara, Y. Alternative pathway of H2S and polysulfides production from sulfurated catalytic-cysteine of reaction intermediates of 3-mercaptopyruvate sulfurtransferase. Biochem. Biophys. Res. Commun. 2018, 496, 648–653.
- 20. Miyamoto, R.; Koike, S.; Takano, Y.; Shibuya, N.; Kimura, Y.; Hanaoka, K.; Urano, Y.; Ogasawara, Y.; Kimura, H. Polysulfides (H2Sn) produced from the interaction of hydrogen sulfide (H2S) and nitric oxide (NO) activate TRPA1 channels. Sci. Rep. 2017, 7, 45995.
- Kharma, A.; Grman, M.; Misak, A.; Domínguez-Álvarez, E.; Nasim, M.J.; Ondrias, K.; Chovanec, M.; Jacob, C. Inorganic Polysulfides and Related Reactive Sulfur–Selenium Species from the Perspective of Chemistry. Molecules 2019, 24, 1359.
- 22. Koike, S.; Kawamura, K.; Kimura, Y.; Shibuya, N.; Kimura, H.; Ogasawara, Y. Analysis of endogenous H2S and H2Sn in mouse brain by high-performance liquid chromatography with fluorescence and tandem mass spectrometric detection. Free Radic. Biol. Med. 2017, 113, 355–362.
- 23. Nagai, Y.; Tsugane, M.; Oka, J.; Kimura, H. Hydrogen sulfide induces calcium waves in astrocytes. FASEB J. 2004, 18, 557–559.
- 24. Wang, L.; Cvetkov, T.L.; Chance, M.R.; Moiseenkova-Bell, V.Y. Identification of in Vivo Disulfide Conformation of TRPA1 Ion Channel. J. Biol. Chem. 2012, 287, 6169–6176.
- 25. Hatakeyama, Y.; Takahashi, K.; Tominaga, M.; Kimura, H.; Ohta, T. Polysulfide Evokes Acute Pain through the Activation of Nociceptive TRPA1 in Mouse Sensory Neurons. Mol. Pain 2015, 11, 24.
- 26. Mustafa, A.K.; Gadalla, M.M.; Sen, N.; Kim, S.; Mu, W.; Gazi, S.K.; Barrow, R.K.; Yang, G.; Wang, R.; Snyder, S.H. H2S Signals Through Protein S-Sulfhydration. Sci. Signal. 2009, 2, ra72.
- 27. Mishanina, T.V.; Libiad, M.; Banerjee, R. Biogenesis of reactive sulfur species for signaling by hydrogen sulfide oxidation pathways. Nat. Chem. Biol. 2015, 11, 457–464.
- 28. Hosoki, R.; Matsuki, N.; Kimura, H. The Possible Role of Hydrogen Sulfide as an Endogenous Smooth Muscle Relaxant in Synergy with Nitric Oxide. Biochem. Biophys. Res. Commun. 1997, 237, 527–531.
- 29. Teague, B.; Asiedu, S.; Moore, P.K. The smooth muscle relaxant effect of hydrogen sulphide in vitro: Evidence for a physiological role to control intestinal contractility. Br. J. Pharmacol. 2002, 137, 139–145.
- Whiteman, M.; Li, L.; Kostetski, I.; Chu, S.H.; Siau, J.L.; Bhatia, M.; Moore, P.K. Evidence for the formation of a novel nitrosothiol from the gaseous mediators nitric oxide and hydrogen sulphide. Biochem. Biophys. Res. Commun. 2006, 343, 303–310.
- Filipovic, M.R.; Miljkovic, J.; Allgauer, A.; Chaurio, R.; Shubina, T.; Herrmann, M.; Ivanovic-Burmazovic, I. Biochemical insight into physiological effects of H2S: Reaction with peroxynitrite and formation of a new nitric oxide donor, sulfinyl nitrite. Biochem. J. 2012, 441, 609–621.
- 32. Eberhardt, M.; Dux, M.; Namer, B.; Miljkovic, J.; Cordasic, N.; Will, C.; Kichko, T.I.; De La Roche, J.; Fischer, M.J.; Suárez, S.A.; et al. H2S and NO cooperatively regulate vascular tone by activating a neuroendocrine HNO–TRPA1– CGRP signaling pathway. Nat. Commun. 2014, 5, 4381.
- 33. Cortese-Krott, M.M.; Kuhnle, G.G.C.; Dyson, A.; Fernandez, B.O.; Grman, M.; Dumond, J.F.; Barrow, M.P.; McLeod, G.; Nakagawa, H.; Ondrias, K.; et al. Key bioactive reaction products of the NO/H2S interaction are S/N-hybrid species,

polysulfides, and nitroxyl. Proc. Natl. Acad. Sci. USA 2015, 112, E4651-E4660.

- Bogdándi, V.; Ditrói, T.; Bátai, I.Z.; Sándor, Z.; Minnion, M.; Vasas, A.; Galambos, K.; Buglyó, P.; Pintér, E.; Feelisch, M.; et al. Nitrosopersulfide (SSNO–) Is a Unique Cysteine Polysulfidating Agent with Reduction-Resistant Bioactivity. Antioxid. Redox Signal. 2020, 33, 1277–1294.
- 35. Zhao, W.; Zhang, J.; Lu, Y.; Wang, R. The vasorelaxant effect of H2S as a novel endogenous gaseous KATP channel opener. EMBO J. 2001, 20, 6008–6016.
- Mustafa, A.K.; Sikka, G.; Gazi, S.K.; Steppan, J.; Jung, S.M.; Bhunia, A.K.; Barodka, V.M.; Gazi, F.K.; Barrow, R.K.; Wang, R.; et al. Hydrogen Sulfide as Endothelium-Derived Hyperpolarizing Factor Sulfhydrates Potassium Channels. Circ. Res. 2011, 109, 1259–1268.
- Chen, G.F.; Cheung, D.W. Characterization of acetylcholine-induced membrane hyperpolarization in endothelial cells. Circ. Res. 1992, 70, 257–263.
- Eckman, D.M.; Frankovich, J.D.; Keef, K.D. Comparison of the actions of acetylcholine and BRL 38227 in the guineapig coronary artery. Br. J. Pharmacol. 1992, 106, 9–16.
- 39. Garland, C.; Plane, F.; Kemp, B.K.; Cocks, T.M. Endothelium-dependent hyperpolarization: A role in the control of vascular tone. Trends Pharmacol. Sci. 1995, 16, 23–30.
- 40. Shibuya, N.; Mikami, Y.; Kimura, Y.; Nagahara, N.; Kimura, H. Vascular Endothelium Expresses 3-Mercaptopyruvate Sulfurtransferase and Produces Hydrogen Sulfide. J. Biochem. 2009, 146, 623–626.
- Shibuya, N.; Tanaka, M.; Yoshida, M.; Ogasawara, Y.; Togawa, T.; Ishii, K.; Kimura, H. 3-Mercaptopyruvate Sulfurtransferase Produces Hydrogen Sulfide and Bound Sulfane Sulfur in the Brain. Antioxid. Redox Signal. 2009, 11, 703–714.
- 42. Earley, S. TRPA1 channels in the vasculature. Br. J. Pharmacol. 2012, 167, 13-22.
- 43. Kimura, Y.; Kimura, H. Hydrogen sulfide protects neurons from oxidative stress. FASEB J. 2004, 18, 1165–1167.
- 44. Kimura, Y.; Goto, Y.-I.; Kimura, H. Hydrogen Sulfide Increases Glutathione Production and Suppresses Oxidative Stress in Mitochondria. Antioxid. Redox Signal. 2010, 12, 1–13.
- 45. Kimura, Y.; Dargusch, R.; Schubert, D.; Kimura, H. Hydrogen Sulfide Protects HT22 Neuronal Cells from Oxidative Stress. Antioxid. Redox Signal. 2006, 8, 661–670.
- Elrod, J.W.; Calvert, J.W.; Morrison, J.; Doeller, J.E.; Kraus, D.W.; Tao, L.; Jiao, X.; Scalia, R.; Kiss, L.; Szabo, C.; et al. Hydrogen sulfide attenuates myocardial ischemia-reperfusion injury by preservation of mitochondrial function. Proc. Natl. Acad. Sci. USA 2007, 104, 15560–15565.
- 47. Cooper, A.J.L. Biochemistry of Sulfur-Containing Amino Acids. Annu. Rev. Biochem. 1983, 52, 187–222.
- 48. Shibuya, N.; Koike, S.; Tanaka, M.; Ishigami-Yuasa, M.; Kimura, Y.; Ogasawara, Y.; Fukui, K.; Nagahara, N.; Kimura, H. A novel pathway for the production of hydrogen sulfide from D-cysteine in mammalian cells. Nat. Commun. 2013, 4, 1366.
- 49. Hylin, J.W.; Wood, J.L. Enzymatic Formation of Polysulfides from Mercaptopyruvate. J. Biol. Chem. 1959, 234, 2141–2144.
- 50. Landry, A.P.; Ballou, D.P.; Banerjee, R. H2S oxidation by nanodisc-embedded human sulfide quinone oxidoreductase. J. Biol. Chem. 2017, 292, 11641–11649.
- 51. Vitvitsky, V.; Kabil, O.; Banerjee, R. High Turnover Rates for Hydrogen Sulfide Allow for Rapid Regulation of Its Tissue Concentrations. Antioxid. Redox Signal. 2012, 17, 22–31.
- 52. Searcy, D.; Whitehead, J.; Maroney, M. Interaction of Cu, Zn Superoxide Dismutase with Hydrogen Sulfide. Arch. Biochem. Biophys. 1995, 318, 251–263.
- 53. Searcy, D.G. HS-: O2 oxidoreductase activity of Cu, Zn superoxide dismutase. Arch. Biochem. Biophys. 1996, 334, 50–58.
- Olson, K.R.; Gao, Y.; Arif, F.; Arora, K.; Patel, S.; DeLeon, E.R.; Sutton, T.R.; Feelisch, M.; Cortese-Krott, M.; Straub, K.D. Metabolism of hydrogen sulfide (H2S) and Production of Reactive Sulfur Species (RSS) by superoxide dismutase. Redox Biol. 2018, 15, 74–85.
- 55. Olson, K.R.; Gao, Y.; DeLeon, E.R.; Arif, M.; Arif, F.; Arora, N.; Straub, K.D. Catalase as a sulfide-sulfur oxidoreductase: An ancient (and modern?) regulator of reactive sulfur species (RSS). Redox Biol. 2017, 12, 325–339.
- Akaike, T.; Ida, T.; Wei, F.-Y.; Nishida, M.; Kumagai, Y.; Alam, M.; Ihara, H.; Sawa, T.; Matsunaga, T.; Kasamatsu, S.; et al. Cysteinyl-tRNA synthetase governs cysteine polysulfidation and mitochondrial bioenergetics. Nat. Commun. 2017, 8, 1177.

- 57. Nakamura, S.; Nakamura, M.; Yamazaki, I.; Morrison, M. Reactions of ferryl lactoperoxidase (compound II) with sulfide and sulfhydryl compounds. J. Biol. Chem. 1984, 259, 7080–7085.
- 58. Garai, D.; Ríos-González, B.B.; Furtmüller, P.G.; Fukuto, J.M.; Xian, M.; López-Garriga, J.; Obinger, C.; Nagy, P. Mechanisms of myeloperoxidase catalyzed oxidation of H2S by H2O2 or O2 to produce potent protein Cys–polysulfideinducing species. Free Radic. Biol. Med. 2017, 113, 551–563.
- 59. Warenycia, M.W.; Goodwin, L.R.; Francom, D.M.; Dieken, F.P.; Kombian, S.B.; Reiffenstein, R.J. Dithiothreitol liberates non-acid labile sulfide from brain tissue of H2S-poisoned animals. Arch. Toxicol. 1990, 64, 650–655.
- 60. Ogasawara, Y.; Ishii, K.; Togawa, T.; Tanabe, S. Determination of Bound Sulfur in Serum by Gas Dialysis/High-Performance Liquid Chromatography. Anal. Biochem. 1993, 215, 73–81.
- 61. Ogasawara, Y.; Isoda, S.; Tanabe, S. Tissue and Subcellular Distribution of Bound and Acid-Labile Sulfur, and the Enzymic Capacity for Sulfide Production in the Rat. Biol. Pharm. Bull. 1994, 17, 1535–1542.
- 62. Ishigami, M.; Hiraki, K.; Umemura, K.; Ogasawara, Y.; Ishii, K.; Kimura, H. A Source of Hydrogen Sulfide and a Mechanism of Its Release in the Brain. Antioxid. Redox Signal. 2009, 11, 205–214.
- 63. Go, Y.-M.; Jones, D.P. The Redox Proteome. J. Biol. Chem. 2013, 288, 26512–26520.
- 64. Jarosz, A.P.; Wei, W.; Gauld, J.W.; Auld, J.; Özcan, F.; Aslan, M.; Mutus, B. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is inactivated by S-sulfuration in vitro. Free Radic. Biol. Med. 2015, 89, 512–521.
- 65. Zivanovic, J.; Kouroussis, E.; Kohl, J.B.; Adhikari, B.; Bursac, B.; Schott-Roux, S.; Petrovic, D.; Miljkovic, J.L.; Thomas-Lopez, D.; Jung, Y.; et al. Selective Persulfide Detection Reveals Evolutionarily Conserved Antiaging Effects of S-Sulfhydration. Cell Metab. 2019, 30, 1152–1170.e13.
- 66. Nagahara, N.; Nirasawa, T.; Yoshii, T.; Niimura, Y. Is Novel Signal Transducer Sulfur Oxide Involved in the Redox Cycle of Persulfide at the Catalytic Site Cysteine in a Stable Reaction Intermediate of Mercaptopyruvate Sulfurtransferase? Antioxid. Redox Signal. 2012, 16, 747–753.

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