An Update on Thiol Signaling: S-Nitrosothiols, Hydrogen Sulfide and a Putative Role for Thionitrous Acid

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Abstract: Long considered vital to antioxidant defenses, thiol chemistry has more recently been recognized to be of fundamental importance to cell signaling. S-nitrosothiols—such as S-nitrosoglutathione (GSNO)—and hydrogen sulfide (H2S) are physiologic signaling thiols that are regulated enzymatically. Current evidence suggests that they modify target protein function primarily through post-translational modifications. GSNO is made by NOS and other metalloproteins; H2S by metabolism of cysteine, homocysteine and cystathionine precursors. GSNO generally acts independently of NO generation and has a variety of gene regulatory, immune modulator, vascular, respiratory and neuronal effects. Some of this physiology is shared with H2S, though the mechanisms differ. Recent evidence also suggests that molecules resulting from reactions between GSNO and H2S, such as thionitrous acid (HSNO), could also have a role in physiology. Taken together, these data suggest important new potential targets for thiol-based drug development.

Keywords: S-nitrosothiols; hydrogen sulfide; thionitrous acid; antioxidants

1. Introduction

Thiol chemistry has recently been recognized to be important for the regulation of cell signaling processes. S-nitrosoglutathione (GSNO) and other S-nitrosothiols, as well as hydrogen sulfide (H2S), are enzymatically-regulated cell signaling thiols, affecting target protein function through post-translational modifications. Regulation of the metabolism of GSNO, of other S-nitrosothiols and of H2S (Figure 1) are vital to immune, vascular, respiratory and neuronal signaling. Here, we will review data regarding the role and regulation of these molecules in physiology.
At the myoendothelial junction, eNOS is colocalized with somatic cell hemoglobin alpha [20]. When the
These are neuronal (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS). Activation of all
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Figure 1. Eukaryotic thiol chemistry and the generation of thiol-based signaling molecules. Orange highlight shows product signaling molecules. AKR1A1—aldoketoreductase family 1 member 1A, CAT—cysteine aspartate aminotransferase, CBS—cystathionine b-synthase, CSE—cystathionine gamma lyase, CDO—cysteine deoxygenase, CoA—Coenzyme A, C-SNO—S-nitrosocysteine, GSNO—S-nitrosoglutathione, GSNOR—S-nitrosoglutathione reductase, GS—glutathione synthase, GCS—glutamylcysteine synthase, MAT—methionine adenosyltransferase; SAM—S-adenosyl methionine; 3MST—3 mercaptopuruvate sulfur transferase, PTA—pantetheinase, SNO-CoA—S-nitroso-Coenzyme A, γGT—γ-glutamyl transpeptidase.

2. Overview of S-Nitrosothiol Metabolism

2.1. Production of S-Nitrosothiols and Other Nitrogen Oxides In Vivo

Nitric oxide synthases (NOS) use the guanidino nitrogen of l-arginine [1–4] to form NO, and GSNO is also often formed when NOS is activated [5–8]. Three principal isoforms of NOS exist [9–11]. These are neuronal (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS). Activation of all three can result in downstream S-nitrosothiol formation [6,9,10,12] (Figure 1). Reactions of NO with thiols are typically kinetically favored to occur through interactions with metalloproteins rather than through inorganic NO oxidation. Typically, they involve NO oxidation to NO$. NO is oxidized by reactions with superoxide and with certain metal ions. NO also reacts with oxygen, but this reaction is third order (third order rate constant ~7 × 10$^3$ L$^2$ mol$^{-2}$ sec$^{-1}$) [13]: The reaction is normally quite slow in physiology because the concentrations of NO in the body gas phase are ~nM. The reaction rate is favored in membranes [14] because the reactants are more soluble in lipid than water. As discussed more below, GSNO and other S-nitrosothiols are typically formed through reactions of NO with iron and copper groups in these metalloproteins (including NOSs), though there is evidence also for formation of a complex with an amine of NOS-bound tetrahydrobiopterin (BH$_4$) [15] and other reactions [16]. Other metalloproteins involved in S-nitrosothiol formation include Hb, where S-nitrosylation occurs at the b-93 cysteine [17], and ceruloplasmin [18].

Endothelial NOS provides an example of the role of S-nitrosothiol formation and NO in biology [19–21]. We and others have shown that eNOS activation can result in S-nitrosothiol formation [12,22]. Moreover, GSNO catabolism by GSNO reductase is required to reverse and or modulate the effects of eNOS, suggesting that, in physiology, GSNO is a regulated eNOS product [19,23]. At the myoendothelial junction, eNOS is colocalized with somatic cell hemoglobin alpha [20]. When the iron of the hemoglobin is oxidized, eNOS activation produces NO and S-nitrosothiols; when it is
reduced, inert nitrate is formed [22]. Note that impaired activity of eNOS resulting from oxidative stress in the endothelium involves BH₄ oxidation [24,25]. This induces the uncoupling of eNOS, with consequent generation of O₂⁻ instead of NO [24,26] or GSNO [12]. Endothelial NOS redox chemistry, with products including thiol-stabilized S-nitrosothiols, inert nitrite and nitrate and highly ONOOH, are relevant to a range of vascular diseases [25–36].

2.2. S-Nitrosylation Signaling and S-Nitrosothiols

Broadly, thiols modified by a NO⁺ (RS−•NO⁺), NO− (R-S⁺−NO⁻) or NO (RS-NO) are referred to as S-nitrosothiols [27]. The thiol R group can be a simple proton (thionitrous acid, see below), or can be an amino acid, peptide or protein. S-Nitrosylation is a normally a targeted, post-translational protein cysteine modification with a specific biological purpose. Note that S-nitrosylated proteins may transfer NO to other proteins [28–30]. S-nitrosylation is regulated as a signaling reaction. [5,12,31,32]. Regulation of human airway tone provides an example. GSNO is normally present in the human airway at ~500 nM (30), the IC₅₀ for soluble guanylate cyclase (sGC)-independent human airway dilatation [33]. GSNO prevents β2 agonist tachyphylaxis by S-nitrosylating GRK2 downstream of eNOS activation through its effect on β arrestin to [19]. Indeed, tachyphylaxis to β2-AR agonists is ablated in [19,34] mice lacking the ability to reduce GSNO because of deletion of the enzyme, GSNO reductase (GSNOR). These mice are protected from β-AR [34], and humans with gain-of-function in this enzyme are at increased asthma risk [35].

There are many additional examples of signaling caused by GSNO and other S-nitrosothiols [5,6,12,31,32,36]. These molecules regulate a broad range of bioactivities, ranging from coagulation and N-methyl-d-aspartate (NMDA) dependent neuronal signaling [37,38]. In many cases, NO⁺ is transferred from a low-mass S-nitrosothiol to a protein thiol. A recent example involves S-nitrosylation of connexin 43 (Cx43) hemichannels in the Duchenne Muscular Dystrophy (Dmd) heart that has been driven by β2 agonists to develop stress-induced arrhythmias: inhibition of NOS prevents arrhythmias evoked by isoproterenol [39]. NOS activation results in S-nitrosylation of Cx43 at cysteine 271, regulating arrhythmia risk. [39].

Other mechanisms of thiol modification are relevant as well. Myeloperoxidase causes protein thiol S-nitrosylation at tyrosine-Xn-cysteine (YXnC) motifs in the presence of hydrogen peroxide and nitrite [16]. Inorganic S-nitrosylation can occur at low pH, particularly in the mitochondrial intermembrane space [40], in the lung and gut, and in the blood vessels in ischemic tissues [41,42]. In the case of hemoglobin- and ceruloplasmin-mediated S-nitrosylation, NO radical normally first reduces the metal: Fe³⁺-NO transitions to Fe²⁺-NO⁺; Cu²⁺-NO transitions to Cu⁺-NO⁺. Of note, GSNO can serve as an intermediate to transfer the NO⁺ equivalent from a metalloprotein to a target thiolate.

Note that the GSNO breakdown product, S-nitroso-L-cysteine (L-CSNO), is increasingly appreciated as a stereoselective signaling molecule. L-CSNO was originally considered an endothelium derived relaxing factor (EDRF) [43–46]. Lewis, Bates and others observed that the L-isomers of CSNO and related S-nitrosothiols were substantially more active than the D-isomers, though they evolve NO equally [47–49]. Their findings suggest that L-CSNO activates stereoselective recognition sites [50]. In guinea-pig myocytes, L-CSNO activates large conductance Ca²⁺-activated K⁺-channels by S-nitrosylation of the alpha subunit [51]. In porcine coronary arteries, L-CSNO activates intermediate and small conductance Ca²⁺-activated K⁺-channels. S-nitroso-D-cysteine (D-CSNO) does not have these effects [45,46]. Ca²⁺-activated K⁺-channels activation causes vasorelaxation exclusively from voltage-gated Ca²⁺ channel closures induced by hyperpolarization [52]. Though nifedipine, a voltage-gated Ca²⁺-channel blocker, reduces vasodilator responses from donors of NO, it does not reduce the responses of L-CSNO or the release of EDRF by acetylcholine [52].

Signaling mediated by S-nitrosothiols is not unique to mammalian physiology: it is vital in plant biology and in microbiology. Interaction between eukaryotic host and its microbiome has been shown to be affected by inter-species S-nitrosothiol signaling [53]. For example, prokaryotic
S-nitrosothiol signaling uses the hybrid-cluster protein Hcp downstream of nitrate reductase. Here, the complex interactions of S-nitrosothiol synthases and transnitrosylases signal E. Coli mobility and metabolism [36].

2.3. Denitrosylation

Like other post-translational modifications, S-nitrosylation signaling is balanced by the reverse effect, denitrosylation. Many enzymes function as denitrosylases. Commonly, these use NAD(P)H oxidation to reduce S-nitrosothiols. Examples include NADH-dependent GSNO reductase (see below) and NADPH-dependent SNO-Coenzyme A reductase (Figure 1). Many additional enzyme systems catabolize GSNO, the details of which are beyond the scope of this review [54–60] Products can include another S-nitrosothiols, NO, ONOOH, NH$_2$OH and NH$_3$. SNO-CoA reductase is also known as aldo-keto reductase family 1 member A1 (AKR1A1) (Figure 1). AKR1A1 can catabolize both SNO-CoA and GSNO [61].

These S-nitrosothiol catabolic enzymes play critical roles in human physiology. For example, GSNOR gene variants affect asthma prevalence and β2 agonist responsiveness in specific human asthma subpopulations [35,62,63]; we have identified a specific severe asthmatic population phenotype associated with high GSNOR activity [64]. Denitrosylation functions are vital, as evidenced by functional redundancy. For example, GSNOR $^{-/-}$ mice have more AKR1A1 GSNO catabolic activity than do wild type mice [61].

3. Hydrogen Sulfide Production and Metabolism In Vivo. Similarities and Differences of NO and H$_2$S Metabolism

Like GSNO, H$_2$S is a thiol-based mediator that is produced enzymatically and is active in physiology at low, endogenous concentrations [65–67]. Hydrogen sulfide is produced by mammalian enzymes cystathione-lyase(CSE), cystathione-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (3-MST) [68]. Additionally, cysteine aminotransferase (CAT) produces 3-mercaptopyruvate substrate for 3MST to produce a protein-bound persulfide, that in turn can be reduced to form H$_2$S [69,70] (Figure 1), and, in plants, by desulphydrases [71]. Note that CBS and CSE are multifunctional enzymes catalyzing a range of β replacement and α, β and γ elimination reactions: Their roles in thiol chemistry can often be redundant (Figure 1). The substrate for 3MST is 3-mercaptopyruvate; others can use L-cysteine, cystathione and other substrates (Figure 1).

As with S-nitrosothiol-based signaling, H$_2$S can affect physiology by causing post-translational modifications of protein thiols. Also as with S-nitrosothiols, specific enzymes also break down H$_2$S [72]. For example, mitochondrial rhodanese, a sulfur transferase, catalyzes H$_2$S oxidation [73], as a component of a major H$_2$S catabolic pathway that also involves a sulfide quinone oxido-reductase (SQR) and a sulfur dioxygenase. H$_2$S catabolic enzymes are extensively reviewed in ref [74]. Additionally, iron-containing proteins, such as hemoglobin and cytochrome C oxidase, also can serve as sinks for H$_2$S (71,77).

The first physiological protein target identified for H$_2$S involved vasodilatation mediated by H$_2$S modification of the K$_{ATP}$ (Kir6.x) channel [75]. Like S-nitrosothiols, H$_2$S also acts through post-translational modifications of protein. The key reaction is defined as S-sulfhydration [76,77], the forming protein –SSH moieties. This S-sulfhydration reactions can modify a large number of proteins, including GAPDH (at Cys150), albumin, actin, ADH1, AST, catalase and thioredoxin-reductase [76]. Indeed, there could well be cross-talk between S-nitrosylation and S-sulfhydration signaling [78].

Inhibition of NOS by the nonspecific inhibitor L-NAME leads to inhibition of H2S-induced vasodilation [79–81], while the deletion of CSE (cystathionine γ-lyase) enhances the vasodilatory effects of acetylcholine [82].

Like S-nitrosothiols, H$_2$S signaling has a role in regulating vascular tone. CSE$^{-/-}$ mice have increased blood pressure as they age [83]. Isolated vessels from CSE$^{-/-}$ mice have significantly
impaired methacholine-induced vasodilatation. Of note, activation of endothelial CSE and eNOS are both Ca$^{2+}$-calmodulin dependent [83,84]; and both can involve cGMP and phosphodiesterases, with competing effects. [85,86].

In contrast to some of the more labile S-nitrosothiols; however, H$_2$S is relatively stable in certain body compartments. However, it can be metabolized by methylation or oxidation, and its products excreted in urine [87,88]. It is also is scavenged by its reactions with heme. H$_2$S for example, because of its interaction with mitochondrial cytochrome c oxidase [67,89], can be toxic at higher concentrations [90,91]. Two H$_2$S oxidative pathways have been identified recently and involve cytosolic ferric (met) hemoglobin (Hb) in red blood cells [92] and myoglobin (Mb) in the heart [93]. Both of these proteins have the capability to generate heme-bound polysulfides and free thiosulfates as end-products. Decreasing pH (across the range 8–6.8) decreases heme H$_2$S affinity by causing a right-shift in the binding of H$_2$S to metHb. Equilibrium dissociation constants of metHb and H$_2$S are in the range of 0.26–1.08 µM, which is well below that for NO it (~100 µM) [94] and CN$^-$ (~10 µM) [95], among other metHb ligands. This indicated that H$_2$S is a high-afﬁnity metHb ligand. Rate constants for metHb (3.2 × 10$^{3}$M$^{-1}$s$^{-1}$) [37] and metMb (1.6 × 10$^{4}$M$^{-1}$s$^{-1}$) [96] suggest that metHb is a reversible H$_2$S carrier, affecting H$_2$S bioactivities [95].

Thionitrous Acid and Related Compounds

Thionitrous acid (HSNO) is another low molecular weight thiol that may be relevant to signaling. HSNO can be formed by reactions between hydrogen sulfide (H$_2$S) and S-nitrosothiols [97–99]. For example, HSNO is produced rapidly according to, H$_2$S + GSNO → HSNO + GSH. Theoretically, HSNO can also be formed by the reaction N$_2$O$_3$ → HSNO + HNO$_2$. However, as noted above, N$_2$O$_3$ is not formed abundantly in most physiological systems.

It has been shown that the NaHS/GSNO reaction products relax precontracted rat aortic rings with pharmacology consistent with the relevance of HSNO or SNO-intermediates. These are dependent on heme concentrations, as well as pH [100]. Of note, there is evidence that HSNO can diffuse through membranes to signal in physiology [98], supporting a possible role as a signaling molecule. Note, however, that the pKa of HSNO is low, and HSNO in physiology may exist as the SNO$^-$ anion. A molecule, QT490, has been developed that forms HSNO and provides insight into formation of HSNO/RSNO from the reaction between H$_2$S/RSH and NO in the biological system [101]. It is also possible that HNO and HSSH could be formed from HSNO with H$_2$S. The resulting S–N bond is the longest reported S–N bond for an R-SNO compound, 1.84 Å [102]. The tautomeric form of HSNO is more thermodynamically feasible and kinetically accessible [103]. These reactions could also form bioactive nitroxyl HNO [103]. HNO is a powerful vasodilator. While NO reacts slowly with thiols, the reaction of HNO with thiols is very fast and it depends on the pKa of the reacting thiolate [104]. Rapid HNO production can also occur in small-to-medium-sized sensory neurons and axons, where it was observed to be co-expression of CBS (cystathionine beta synthase) with TRPA1 (transient receptor potential channel A1) [79]. TRPA1 is the Ca$^{2+}$ ion channel responsible for CGRP release induced by HNO, [79] which is known to be co-expressed with nNOS. Reactive cysteine residues on TRPA1 become oxidized by HNO, resulting in long-lasting channel opening, Ca$^{2+}$ influx, and subsequent release of CGRP [105]. These three proteins, CBS, nNOS, and TRPA1, represent a functional unit that is involved in the regulation of peripheral blood flow [106] and even the regulation of systemic blood pressure [79] It has been hypothesized that the disturbances in the regulation of this pathway might be responsible for the migraine attacks [106].

Taken together, these data suggest the possible relevance of HSNO at the interface of S-nitrosothiol and H$_2$S signaling.

4. Conclusions

Small thiol molecules have cell signaling effects in physiological concentrations. Both S-nitrosothiols and H$_2$S can be formed and broken down by specific regulatory proteins.
Both have physiological effects involving post-translational modifications, primarily at cysteine residues, but the mechanisms are different. Once considered primarily valuable for breaking disulfide bonds to reduce viscosity and/or to augment antioxidant defenses, thiol chemistry is beginning to be recognized as relevant to cell signaling reactions. These recent observations suggest that thiol chemistry may be more useful than previously thought for new drug development.

However, more work needs to be done to understand in greater details the roles of S-nitrosothiols and of H₂S in physiology, and to determine the degree to which HSNO chemistry is relevant to biology.

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**Abbreviations**

AKR1A1—aldoketoreductase family 1 member 1A, CAT—cysteine aspartate aminotransferase, CBS—cystathione b—synthase, CSE—cystathione gamma lyase, CDO—cysteine deoxygenase, CoA—Coenzyme A, C-SNO—S-nitrosocysteine, GSNO—S-nitrosoglutathione, GSNOR—S-nitrosoglutathione reductase, GS—glutathione synthase, GCS—glutamylcysteine synthase, MAT—methionine adenosyltransferase; SAM—S-adenosyl methionine; 3MST—3 mercaptopuruvate sulfur transferase, PTA—pantetheinase, SNO-CoA—S-nitroso-Coenzyme A, γGT—γ-glutamyl transpeptidase.

**References**

1. Hibbs, J.B., Jr.; Vavrin, Z.; Taintor, R.R. L-arginine is required for expression of the activated macrophage effector mechanism causing selective metabolic inhibition in target cells. *J. Immunol.* 1987, 138, 550–565. [PubMed]
2. Babu, B.R.; Frey, C.; Griffth, O.W. L-arginine binding to nitric-oxide synthase. The role of H-bonds to the nonreactive guanidinium nitrogens. *J. Biol. Chem.* 1999, 274, 25218–25226. [CrossRef] [PubMed]
3. Southan, G.J.; Srinivasan, A. Nitrogen oxides and hydroxyguanidines: Formation of donors of nitric and nitrous oxides and possible relevance to nitrous oxide formation by nitric oxide synthase. *Nitric Oxide* 1998, 2, 270–286. [CrossRef] [PubMed]
4. Vicente, F.B.; Vespa, G.; Miller, A.; Haymond, S. Quantification of Arginine and Its Methylated Derivatives in Plasma by High-Performance Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS). *Methods Mol. Biol.* 2016, 1378, 21–30. [CrossRef] [PubMed]
5. Marozkina, N.V.; Gaston, B. S-Nitrosylation signaling regulates cellular protein interactions. *Biochim. Biophys. Acta* 2012, 1820, 722–729. [PubMed]
6. Marozkina, N.V.; Gaston, B. Nitrogen chemistry and lung physiology. *Annu. Rev. Physiol.* 2015, 77, 431–452. [CrossRef]
7. Smith, B.C.; Marletta, M.A. Mechanisms of S-nitrosothiol formation and selectivity in nitric oxide signaling. *Curr. Opin. Chem. Biol.* 2012, 16, 498–506. [CrossRef]
8. Blonder, J.P.; Mutka, S.C.; Sun, X.; Qiu, J.; Green, L.H.; Mehra, N.K.; Boyanapalli, R.; Suniga, M.; Look, K.; Delany, C.; et al. Pharmacologic inhibition of S-nitrosoglutathione reductase protects against experimental asthma in BALB/c mice through attenuation of both bronchoconstriction and inflammation. *BMC Pulm. Med.* 2014, 14, 3. [CrossRef]
9. Kobzik, L.; Bredt, D.S.; Lowenstein, C.J.; Drazen, J.; Gaston, B.; Sugarbaker, D.; Stamler, J.S. Nitric oxide synthase in human and rat lung: Immunocytochemical and histochemical localization. *Am. J. Respir. Cell Mol. Biol.* 1993, 9, 371–377. [CrossRef]
10. Asano, K.; Chee, C.B.; Gaston, B.; Lilly, C.M.; Gerard, C.; Drazen, J.M.; Stamler, J.S. Constitutive and inducible nitric oxide synthase gene expression, regulation, and activity in human lung epithelial cells. *Proc. Natl. Acad. Sci. USA* 1994, 91, 10089–10093.
11. Guo, F.H.; De Raeve, H.R.; Rice, T.W.; Stuehr, D.J.; Thunnissen, F.B.; Erzurum, S.C. Continuous nitric oxide synthesis by inducible nitric oxide synthase in normal human airway epithelium in vivo. *Proc. Natl. Acad. Sci. USA* 1995, 92, 7809–7813. [PubMed]
12. Gow, A.J.; Chen, Q.; Hess, D.T.; Day, B.J.; Ischiropoulos, H.; Stamler, J.S. Basal and stimulated protein S-nitrosylation in multiple cell types and tissues. *J. Biol. Chem.* 2002, 277, 9637–9640. [CrossRef] [PubMed]
13. Tsukahara, H.; Ishida, T.; Mayumi, M. Gas-phase oxidation of nitric oxide: Chemical kinetics and rate constant. *Nitric Oxide* 1999, 3, 191–198. [CrossRef] [PubMed]
14. Liu, X.; Miller, M.J.; Joshi, M.S.; Thomas, D.D.; Lancaster, J.R., Jr. Accelerated reaction of nitric oxide with O2 within the hydrophobic interior of biological membranes. *Proc. Natl. Acad. Sci. USA* 1998, 95, 2175–2179.
15. Rosenfeld, R.J.; Bonaventura, J.; Szymczyna, B.R.; MacCoss, M.J.; Arvai, A.S.; Yates, J.R., III; Tainer, J.A.; Getzoff, E.D. Nitric-oxide synthase forms N-NO-pterin and S-NO-cys: Implications for activity, allosteric, and regulation. *J. Biol. Chem.* 2010, 285, 31581–31589. [CrossRef]
16. Zhang, H.; Xu, Y.; Joseph, J.; Kalyanaraman, B. Intramolecular electron transfer between tyrosyl radical and cysteine residue inhibits tyrosine nitration and induces thyl radical formation in model peptides treated with myeloperoxidase, H2O2, and NO2-: EPR SPIN trapping studies. *J. Biol. Chem.* 2005, 280, 40684–40698. [CrossRef]
17. Stamler, J.S.; Jia, L.; Eu, J.P.; Demchenko, I.T.; Bonaventura, J.; Gernert, K.; Piantadosi, C.A. Blood Flow Regulation by S-Nitrosohemoglobin in the Physiological Oxygen Gradient. *Science* 1997, 276, 2034–2037. [CrossRef]
18. Inoue, K.; Akaike, T.; Miyamoto, Y.; Okamoto, T.; Sawa, T.; Otagiri, M.; Suzuki, S.; Yoshimura, T.; Maeda, H. Nitrosothiol formation catalyzed by ceruloplasmin. Implication for cytoprotective mechanism in vivo. *J. Biol. Chem.* 1999, 274, 27069–27075.
19. Francis, S.H.; Busch, J.L.; Corbin, J.D.; Sibley, D. cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. *Pharmacol. Rev.* 2010, 62, 525–563. [CrossRef]
20. Mason, M.G.; Nicholls, P.; Wilson, M.T.; Cooper, C.E. Nitric oxide inhibition of respiration involves both competitive (heme) and noncompetitive (copper) binding to cytochrome c oxidase. *Proc. Natl. Acad. Sci. USA* 2006, 103, 708–713. [CrossRef]
21. Whalen, E.J.; Foster, M.W.; Matsumoto, A.; Ozawa, K.; Violin, J.D.; Que, L.G.; Nelson, C.D.; Benhar, M.; Keys, J.R.; Rockman, H.A.; et al. Regulation of beta-adrenergic receptor signaling by S-nitrosylation of G-protein-coupled receptor kinase 2. *Cell* 2007, 129, 511–522. [CrossRef] [PubMed]
22. Gaston, B.; Drazen, J.M.; Jansen, A.; Sugarbaker, D.A.; Loscalzo, J.; Richards, W.; Stamler, J.S. Relaxation of human bronchial smooth muscle by S-nitrosothiols in vitro. *J. Pharmacol. Exp. Ther.* 1994, 268, 978–984. [PubMed]
23. Carver, D.J.; Gaston, B.; Deronde, K.; Palmer, L.A. Akt-mediated activation of HIF-1 in pulmonary vascular endothelial cells by S-nitrosoglutathione. *Am. J. Respir. Cell Mol. Biol.* 2007, 37, 255–263. [CrossRef] [PubMed]
24. Straub, A.C.; Lohman, A.W.; Billaud, M.; Johnstone, S.R.; Dwyer, S.T.; Lee, M.Y.; Bortz, P.S.; Best, A.K.; Columbus, L.; Gaston, B.; et al. Endothelial cell expression of haemoglobin alpha regulates nitric oxide synthesis by inducible nitric oxide synthase in normal human airway epithelium in vivo. *Proc. Natl. Acad. Sci. USA* 2005, 102, 191–198. [CrossRef] [PubMed]
25. Palmer, L.A.; Doctor, A.; Chhabra, P.; Sharma, M.L.; Laubach, V.E.; Karlinsky, M.Z.; Forbes, M.S.; Macdonald, T.; Gaston, B. S-nitrosothiol signal hypoxia-mimetic vascular pathology. *J. Clin. Investig.* 2007, 117, 2592–2601. [CrossRef]
26. Antoniades, C.; Shirodaria, C.; Crabtree, M.; Rinze, R.; Alp, N.; Cunnington, C.; Diesch, J.; Toussoulis, D.; Stefanadis, C.; Leeson, P.; et al. Altered plasma versus vascular biopterins in human atherosclerosis reveal relationships between endothelial nitric oxide synthase coupling, endothelial function, and inflammation. *Circulation* 2007, 116, 2851–2859. [CrossRef]
27. Antoniades, C.; Tousoulis, D.; Stefanadis, C. Effects of endothelial nitric oxide synthase gene polymorphisms on oxidative stress, inflammatory status, and coronary atherosclerosis: An example of a transient phenotype. *J. Am. Coll. Cardiol.* 2007, 49, 1226–1227. [CrossRef]
28. Dikalova, A.; Aschner, J.L.; Kaplowitz, M.R.; Summar, M.; Fike, C.D. Tetrahydrobiopterin oral therapy recouples eNOS and ameliorates chronic hypoxia-induced pulmonary hypertension in newborn pigs. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2016, 311, L743–L753. [CrossRef]
29. Stamler, J.S.; Singel, D.J.; Loscalzo, J. Biochemistry of nitric oxide and its redox-activated forms. *Science* 1992, 258, 1898–1902.
30. Jia, J.; Arif, A.; Terenzi, F.; Willard, B.; Plow, E.F.; Hazen, S.L.; Fox, P.L. Target-selective protein S-nitrosylation by sequence motif recognition. Cell 2014, 159, 623–634. [CrossRef]  
31. Kornberg, M.D.; Sen, N.; Hara, M.R.; Juluri, K.R.; Nguyen, J.V.; Snowman, A.M.; Law, L.; Hester, L.D.; Snyder, S.H. GAPDH mediates nitrosylation of nuclear proteins. Nat. Cell Biol. 2010, 12, 1094–1100. [CrossRef] [PubMed]  
32. Mitchell, D.A.; Marletta, M.A. Thioredoxin catalyzes the S-nitrosation of the caspase-3 active site cysteine. Nat. Chem. Biol. 2005, 1, 154–158. [CrossRef] [PubMed]  
33. Foster, M.W.; Hess, D.T.; Stamler, J.S. Protein S-nitrosylation in health and disease: A current perspective. Trends Mol. Med. 2009, 15, 391–404. [CrossRef] [PubMed]  
34. Paige, J.S.; Xu, G.; Stsiapura, V.I.; Bederman, I.; Stepuro, I.I.; Morozkina, T.S.; Lewis, S.J.; Smith, L.; Gaston, B.; Marozkina, N. Dietary nitrite supplementation protects against myocardial ischemia-reperfusion injury. Proc. Natl. Acad. Sci. USA 2009, 106, 649–654. [CrossRef] [PubMed]  
35. Gaston, B.; Reilly, J.; Drazen, J.M.; Fackler, J.; Ramdev, P.; Arnelle, D.; Mullins, M.E.; Sugarbaker, D.J.; Chee, C.; Singel, D.J.; et al. Endogenous nitrogen oxides and bronchodilator S-nitrosothiols in human airways. Proc. Natl. Acad. Sci. USA 1993, 90, 10957–10961.  
36. Que, L.G.; Liu, L.; Yan, Y.; Whitehead, G.S.; Gavett, S.H.; Schwartz, D.A.; Stamler, J.S. Protection from experimental asthma by an endogenous bronchodilator. Science 2005, 308, 1618–1621. [CrossRef]  
37. Moore, P.E.; Ryckman, K.K.; Williams, S.M.; Patel, N.; Summar, M.L.; Sheller, J.R. Genetic variants of GSNOR and ADRB2 influence response to albuterol in African-American children with severe asthma. Pediatr. Pulmonol. 2009, 44, 649–654. [CrossRef]  
38. Seth, D.; Hess, D.T.; Hausladen, A.; Wang, L.; Wang, Y.J.; Stamler, J.S. A Multiplex Enzymatic Machinery for Cellular Protein S-nitrosylation. Mol. Cell 2018, 69, 451–464. [CrossRef]  
39. Stamler, J.S.; Toone, E.J.; Lipton, S.A.; Sucher, N.J. (S)NO signals: Translocation, regulation, and a consensus motif. Neuron 1997, 18, 691–696.  
40. Choi, Y.B.; Tenneti, L.; Le, D.A.; Ortiz, J.; Bai, G.; Chen, H.S.; Lipton, S.A. Molecular basis of NMDA receptor-coupled ion channel modulation by S-nitrosylation. Nat. Neurosci. 2000, 3, 15–21. [CrossRef]  
41. Lillo, M.A.; Himelman, E.; Shirokova, N.; Xie, L.H.; Fraidenraich, D.; Contreras, J.E. S-nitrosylation of Connexin43 hemichannels elicits cardiac stress induced arrhythmias in Duchenne Muscular Dystrophy mice. JCI Insight 2019, 4, 130091. [CrossRef] [PubMed]  
42. Mannick, J.B.; Schonhoff, C.; Papeta, N.; Ghafoorifar, P.; Szibor, M.; Fang, K.; Gaston, B. S-Nitrosylation of mitochondrial caspases. J. Cell Biol. 2001, 154, 1111–1116. [CrossRef] [PubMed]  
43. Bryan, N.S.; Calvert, J.W.; Elrod, J.W.; Gundewar, S.; Ji, S.Y.; Lefer, D.J. Dietary nitrite supplementation protects against myocardial ischemia-reperfusion injury. Proc. Natl. Acad. Sci. USA 2007, 104, 19144–19149. [CrossRef] [PubMed]  
44. Stsiapura, V.I.; Bederman, I.; Stepuro, I.I.; Morozkina, T.S.; Lewis, S.J.; Smith, L.; Gaston, B.; Marozkina, N. S-Nitrosoglutathione formation at gastric pH is augmented by ascorbic acid and by the antioxidant vitamin complex, Resistin. Pharm. Biol. 2018, 56, 86–93. [CrossRef] [PubMed]  
45. Myers, P.R.; Minor, R.L., Jr.; Gur, R., Jr.; Bates, J.N.; Harrison, D.G. Vasorelaxant properties of the endothelium-derived relaxing factor more closely resemble S-nitrosocysteine than nitric oxide. Nature 1990, 345, 161–163. [CrossRef] [PubMed]  
46. Rosenblum, W.I. Endothelium-derived relaxing factor in brain blood vessels is not nitric oxide. Stroke 1992, 23, 1527–1532. [CrossRef]  
47. Batenburg, W.W.; de Vries, R.; Saxena, P.R.; Danser, A.H. L-S-nitrosothiols: Endothelium-derived hyperpolarizing factors in porcine coronary arteries? J. Hypertens. 2004, 22, 1927–1936. [CrossRef]  
48. Batenburg, W.W.; Popp, R.; Fleming, I.; de Vries, R.; Garrelds, I.M.; Saxena, P.R.; Danser, A.H. Bradykinin-induced relaxation of coronary microarteries: S-nitrosothiols as EDHF? Br. J. Pharmacol. 2004, 142, 125–135. [CrossRef]  
49. Davisson, R.L.; Travis, M.D.; Bates, J.N.; Lewis, S.J. Hemodynamic effects of L- and D-S-nitrosocysteine in the rat. Stereoselective S-nitrosothiol recognition sites. Circ. Res. 1996, 79, 256–262.  
50. Lewis, S.J.; Travis, M.D.; Bates, J.N.; Johnson, A.K.; Lewis, S.J. Stereoselective actions of S-nitrosocysteine in central nervous system of conscious rats. Am. J. Physiol. 1997, 272, H2361–H2368. [CrossRef] [PubMed]
52. Lewis, S.J.; Hoque, A.; Bates, J.N. Differentiation of L- and D-S-nitrosothiol recognition sites in vivo. *J. Cardiovasc. Pharmacol.* 2005, 46, 660–671. [CrossRef] [PubMed]

53. Lang, R.J.; Harvey, J.R.; Mulholland, E.L. Sodium (2-sulfonatoethyl) methanethiosulfonate prevents S-nitroso-cysteine activation of Ca<sup>2+</sup>-activated K<sup>+</sup> (BKCa) channels in myocytes of the guinea-pig taenia caeca. *Br. J. Pharmacol.* 2003, 139, 1153–1163. [CrossRef] [PubMed]

54. Travis, M.D.; Hoque, A.; Bates, J.N.; Lewis, S.J. Blockade of voltage-sensitive Ca(2+)-channels markedly diminishes nitric oxide- but not L-S-nitrosocysteine- or endothelium-dependent vasodilation in vivo. *Eur. J. Pharmacol.* 2000, 408, 289–298. [CrossRef]

55. Seth, P.; Hsieh, P.N.; Jamal, S.; Wang, L.; Gygi, S.P.; Jain, M.K.; Coller, J.; Stamler, J.S. Regulation of MicroRNA Machinery and Development by Interspecies S-Nitrosylation. *Cell* 2019, 176, 1014–1025. [CrossRef]

56. Fang, K.; Johns, R.; Macdonald, T.; Kinter, M.; Gaston, B. S-nitrosoglutathione breakdown prevents airway smooth muscle relaxation in the guinea pig. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2000, 279, L716–L721.

57. Benhar, M.; Forrester, M.T.; Hess, D.T.; Stamler, J.S. Regulated protein denitrosylation by cytosolic and mitochondrial thioredoxins. *Science* 2008, 320, 1050–1054. [CrossRef]

58. Haendeler, J.; Hoffmann, J.; Tischler, V.; Berk, B.C.; Zeiher, A.M.; Dimmeler, S. Redox regulatory and anti-apoptotic functions of thioredoxin depend on S-nitrosoprotein synthesis at cysteine 69. *Nat. Cell Biol.* 2002, 4, 743–749. [CrossRef]

59. Bateman, R.L.; Rauh, D.; Tavshanjian, B.; Shokat, K.M. Human carbonyl reductase 1 is an S-nitrosoglutathione reductase. *J. Biol. Chem.* 2008, 283, 35756–35762.

60. Trujillo, M.; Alvarez, M.N.; Peluffo, G.; Freeman, B.A.; Radi, R. Xanthine oxidase-mediated decomposition of S-nitrosothiols. *J. Biol. Chem.* 1998, 273, 7828–7834.

61. Johnson, M.A.; Macdonald, T.L.; Mannick, J.B.; Conaway, M.R.; Gaston, B. Accelerated S-nitrosothiol breakdown by amyotrophic lateral sclerosis mutant copper, zinc-superoxide dismutase. *J. Biol. Chem.* 2001, 276, 39872–39878. [PubMed]

62. Ramachandran, N.; Root, P.; Jiang, X.M.; Hogg, P.J.; Mutus, B. Mechanism of transfer of NO from extracellular S-nitrosoglutathione into the cytosol by cell-surface protein disulfide isomerase. *Proc. Natl. Acad. Sci. USA* 2001, 98, 9539–9544. [CrossRef] [PubMed]

63. Stomerski, C.T.; Anand, P.; Venetos, N.M.; Hausladen, A.; Zhou, H.L.; Premont, R.T.; Stamler, J.S. AKR1A1 is a novel mammalian S-nitroso-glutathione reductase. *J. Biol. Chem.* 2019, 294, 18285–18293. [CrossRef] [PubMed]

64. Wu, H.; Romieu, I.; Sienna-Monge, J.J.; Estela Del Rio-Navarro, B.; Anderson, D.M.; Jenchura, C.A.; Hi, H.; Ramirez-Agular, M.; Del Carmen Lara-Sanchez, I.; London, S.J. Genetic variation in S-nitrosogluthathione reductase (GSNOR) and childhood asthma. *J. Allergy Clin. Immunol.* 2007, 120, 322–328. [CrossRef] [PubMed]

65. Choudhry, S.; Que, L.G.; Yang, Z.; Liu, L.; Eng, C.; Kim, S.O.; Kumar, G.; Thyne, S.; Chapela, R.; Rodriguez-Santana, J.R.; et al. GSNO reductase and beta2-adrenergic receptor gene-gene interaction: Bronchodilator responsiveness to albuterol. *Pharmacogenet. Genomics* 2010, 20, 351–358. [CrossRef]

66. Marozkina, N.V.; Wang, X.Q.; Stsiapura, V.; Fitzpatrick, A.; Carraro, S.; Hawkins, G.A.; Bleecker, E.; Meyers, D.; Jarjour, N.; Fain, S.B.; et al. Phenotype of asthmatics with increased airway S-nitrosoglutathione reductase activity. *Eur. Respir. J.* 2015, 45, 87–97. [CrossRef]

67. Shen, X.; Kolluru, G.K.; Yuan, S.; Kevil, C.G. Measurement of H2S in vivo and in vitro by the monobromobimane method. *Methods Enzymol.* 2015, 554, 31–45. [CrossRef]

68. Wintner, E.A.; Deckwerth, T.L.; Langston, W.; Bengtsson, A.; Leviten, D.; Hill, P.; Insko, M.A.; Dumpit, R.; VandenEkat, E.; Toombs, C.F.; et al. A monobromobimane-based assay to measure the pharmacokinetic profile of reactive sulphide species in blood. *Br. J. Pharmacol.* 2010, 160, 941–957. [CrossRef]

69. Sonobe, T.; Haouzi, P. H2S concentrations in the heart after acute H2S administration: Methodological and physiological considerations. *Am. J. Physiol. Heart Circ. Physiol.* 2016, 311, H1445–H1458. [CrossRef]

70. Prabhakar, N.R. Carbon monoxide (CO) and hydrogen sulfide (H(2)S) in hypoxic sensing by the carotid body. *Respir. Physiol. Neurobiol.* 2012, 184, 165–169. [CrossRef]

71. Shibuya, N.; Mikami, Y.; Kimura, Y.; Nagahara, N.; Kimura, H. Vascular Endothelium Expresses 3-Mercapto-pyruvate Sulfurtransferase and Produces Hydrogen Sulfide. *J. Biochem.* 2009, 146, 623–626. [CrossRef] [PubMed]
72. Vellecco, V.; Mancini, A.; Ianaro, A.; Calderone, V.; Attanasio, C.; Cantalupo, A.; Andria, B.; Savoia, G.; Panza, E.; Di Martino, A.; et al. Cystathionine beta-synthase-derived hydrogen sulfide is involved in human malignant hyperthermia. Clin. Sci. 2016, 130, 35–44. [CrossRef] [PubMed]
73. Alvarez, C.; Calo, L.; Romero, L.C.; Garcia, I.; Gotor, C. An O-acetylserine(thiol)lyase homolog with L-cysteine desulphydrase activity regulates eye homeostasis in Arabidopsis. Plant Physiol. 2010, 152, 656–669. [CrossRef] [PubMed]
74. Reis, A.; Stern, A.; Monteiro, H.P. S-nitrosothiols and H2S donors: Potential chemo-therapeutic agents in cancer. Redox Biol. 2019, 27, 101190. [CrossRef]
75. Wilson, K.; Mudra, M.; Furne, J.; Levitt, M. Differentiation of the roles of sulfide oxidase and rhodanese in the detoxification of sulfide by the colonic mucosa. Dig. Dis. Sci. 2008, 53, 277–283. [CrossRef]
76. Jackson, M.R.; Melideo, S.L.; Jorns, M.S. Human sulfide:quinone oxidoreductase catalyzes the first step in hydrogen sulfide metabolism and produces a sulfane sulfur metabolite. Biochemistry 2012, 51, 6804–6815. [CrossRef]
77. Zhao, W.; Zhang, J.; Lu, Y.; Wang, R. The vasorelaxant effect of H(2)S as a novel endogenous gaseous K(ATP) channel opener. EMBO J. 2001, 20, 6008–6016. [CrossRef]
78. 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. [CrossRef]
79. Lu, C.; Kavalier, A.; Lukyanov, E.; Gross, S.S. S-sulfhydration/desulfhydration and S-nitrosylation/denitrosylation: A common paradigm for gasotransmitter signaling by HS and NO. Methods 2013, 62, 177–181. [CrossRef]
80. Hara, M.R.; Agrawal, N.; Kim, S.F.; Cascio, M.B.; Fujimuro, M.; Ozeki, Y.; Takahashi, M.; Cheah, J.H.; Tsvetkov, D.; Wang, N.; Rabelo, L.A.; et al. H2S as a physiologic vasorelaxant: Hypertension in mice with deletion of cystathionine gamma-lyase. Arterioscler. Thromb. Vasc. Biol. 2008, 28, 1210–1217. [CrossRef]
81. Eberhardt, M.; Dux, M.; Namer, B.; Miljkovic, J.; Cordasic, N.; Will, C.; Ichikawa, T.; de la Roche, J.; Fischer, M.; Suarez, S.A.; et al. H2S and NO cooperatively regulate vascular tone by activating a neuroendocrine HNO-TRPA1-CGRP signalling pathway. Nat. Commun. 2014, 5, 4381. [CrossRef] [PubMed]
82. 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. [CrossRef] [PubMed]
83. Coletta, C.; Papapetropoulos, A.; Erdelyi, K.; Olah, G.; Modis, K.; Panopoulos, P.; Asimakopoulou, A.; Gero, D.; Sharina, I.; Martin, E.; et al. Hydrogen sulfide and nitric oxide are mutually dependent in the regulation of angiogenesis and endothelium-dependent vasorelaxation. Proc. Natl. Acad. Sci. USA 2012, 109, 9161–9166. [CrossRef] [PubMed]
84. Szijarto, I.A.; Marko, L.; Filipovic, M.R.; Miljkovic, J.L.; Tabeling, C.; Tsvetkov, D.; Wang, N.; Rabelo, L.A.; Wittenrath, M.; Schildberg, A.; et al. Cystathionine gamma-Lyase-Produced Hydrogen Sulfide Controls Endothelial NO Bioavailability and Blood Pressure. Hypertension 2018, 71, 1210–1217. [CrossRef]
85. Yang, G.; Wu, L.; Jiang, B.; Yang, W.; Qi, J.; Cao, K.; Meng, Q.; Mustafa, A.K.; Mu, W.; Zhang, S.; et al. H2S as a physiologic vasorelaxant: Hypertension in mice with deletion of cystathionine gamma-lyase. Science 2008, 322, 587–590. [CrossRef]
86. Cirino, G.; Vellecco, V.; Bucci, M. Nitric oxide and hydrogen sulfide: The gasotransmitter paradigm of the vascular system. Br. J. Pharmacol. 2017, 174, 4021–4031. [CrossRef]
87. Bucci, M.; Papapetropoulos, A.; Vellecco, V.; Zhou, Z.; Pyriochou, A.; Roussos, C.; Roviezzo, F.; Brancaleone, V.; Cirino, G. Hydrogen sulfide is an endogenous inhibitor of phosphodiesterase activity. Arterioscler. Thromb. Vasc. Biol. 2010, 30, 1998–2004. [CrossRef]
88. Bucci, M.; Papapetropoulos, A.; Vellecco, V.; Zhou, Z.; Aidi, A.; Giannogonas, P.; Cantalupo, A.; Dhayade, S.; Karalis, K.P.; Wang, R.; et al. cGMP-dependent protein kinase contributes to hydrogen sulfide-stimulated vasorelaxation. PLoS ONE 2012, 7, e33319. [CrossRef]
89. Wallace, J.L.; Wang, R. Hydrogen sulfide-based therapeutics: Exploiting a unique but ubiquitous gasotransmitter. Nat. Rev. Drug Discov. 2015, 14, 329–345. [CrossRef]
90. Wang, R. Physiological implications of hydrogen sulfide: A whiff exploration that blossomed. Physiol. Rev. 2012, 92, 791–896. [CrossRef]
91. Pietri, R.; Roman-Morales, E.; Lopez-Garriga, J. Hydrogen sulfide and hemeproteins: Knowledge and Mysteries. Antioxid. Redox Signal. 2011, 15, 393–404. [CrossRef] [PubMed]
92. 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. [CrossRef] [PubMed]
93. Olson, K.R.; Straub, K.D. The Role of Hydrogen Sulfide in Evolution and the Evolution of Hydrogen Sulfide in Metabolism and Signaling. *Physiology* 2016, 31, 60–72. [CrossRef] [PubMed]
94. Vitvitsky, V.; Yadav, P.K.; Kurthen, A.; Banerjee, R. Sulfide Oxidation by a Noncanonical Pathway in Red Blood Cells Generates Thiosulfate and Polysulfides. *J. Biol. Chem.* 2015, 290, 8310–8320. [CrossRef] [PubMed]
95. Bostelaar, T.; Vitvitsky, V.; Kumutima, J.; Lewis, B.E.; Yadav, P.K.; Brunold, T.C.; Filippovic, M.; Lehnert, N.; Stemmler, T.L.; Banerjee, R. Hydrogen Sulfide Oxidation by Myoglobin. *J. Am. Chem. Soc.* 2016, 138, 8476–8488. [CrossRef]
96. Sharma, V.S.; Traylor, T.G.; Gardiner, R.; Mizukami, H. Reaction of nitric oxide with heme proteins and model compounds of hemoglobin. *Biochemistry* 1987, 26, 3837–3843. [CrossRef]
97. Jensen, B.; Fago, A. Reactions of ferric hemoglobin and myoglobin with hydrogen sulfide under physiological conditions. *J. Inorg. Biochem.* 2018, 182, 133–140. [CrossRef]
98. Choi, Y.B.; Lipton, S.A. Redox modulation of the NMDA receptor. *Cell. Mol. Life Sci.* 2000, 57, 1535–1541. [CrossRef]
99. Li, Q.; Lancaster, J.R., Jr. Chemical foundations of hydrogen sulfide biology. *Nitric Oxide* 2013, 35, 21–34. [CrossRef]
100. Filipovic, M.R.; Miljkovic, J.L.; Nauser, T.; Royzen, M.; Klos, K.; Shubina, T.; Koppenol, W.H.; Lippard, S.J.; Ivanovic-Burmazovic, I. Chemical characterization of the smallest S-nitrosothiol, HSNO; cellular cross-talk of H2S and S-nitrosothiols. *J. Am. Chem. Soc.* 2012, 134, 12016–12027. [CrossRef] [PubMed]
101. Bruce King, S. Potential biological chemistry of hydrogen sulfide (H2S) with the nitrogen oxides. *Free Radic. Biol. Med.* 2013, 55, 1–7. [CrossRef] [PubMed]
102. Berenyiova, A.; Grman, M.; Miuskovic, A.; Stasko, A.; Misak, A.; Nagy, P.; Ondriasova, E.; Cacanyiova, S.; Brezova, V.; Feelisch, M.; et al. The reaction products of sulfide and S-nitrosoglutathione are potent vasorelaxants. *Nitric Oxide* 2015, 46, 123–130. [CrossRef] [PubMed]
103. Islam, A.S.M.; Bhowmick, R.; Pal, K.; Katarkar, A.; Chaudhuri, K.; Ali, M. A Smart Molecule for Selective Sensing of Nitric Oxide: Conversion of NO to HSNO; Relevance of Biological HSNO Formation. *Inorg. Chem.* 2017, 56, 4324–4331. [CrossRef] [PubMed]
104. Kang, J.; Xu, S.; Radford, M.N.; Zhang, W.; Kelly, S.S.; Day, J.J.; Xian, M. O–S Relay Deprotection: A General Approach to Controllable Donors of Reactive Sulfur Species. *Angew. Chem. Int. Ed. Engl.* 2018, 57, 5893–5897. [CrossRef] [PubMed]
105. Nava, M.; Martin-Drumel, M.A.; Lopez, C.A.; Crabtree, K.N.; Womack, C.C.; Nguyen, T.L.; Thornworth, S.; Cummins, C.C.; Stanton, J.F.; McCarthy, M.C. Spontaneous and Selective Formation of HSNO, a Crucial Intermediate Linking H2S and Nitroso Chemistries. *J. Am. Chem. Soc.* 2016, 138, 11441–11444. [CrossRef] [PubMed]
106. Ivanova, L.V.; Anton, B.J.; Timerghazin, Q.K. On the possible biological relevance of HSNO isomers: A computational investigation. *Phys. Chem. Chem. Phys.* 2014, 16, 8476–8486. [CrossRef] [PubMed]

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