Published in final edited form as:
Biochim Biophys Acta. 2014 August ; 1844(8): 1355–1366. doi:10.1016/j.bbapap.2014.01.002.

H_2S and its role in redox signaling☆,,☆☆

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Abstract

Hydrogen sulfide (H_2S) has emerged as an important gaseous signaling molecule that is produced endogenously by enzymes in the sulfur metabolic network. H_2S exerts its effects on multiple physiological processes important under both normal and pathological conditions. These functions include neuromodulation, regulation of blood pressure and cardiac function, inflammation, cellular energetics and apoptosis. Despite the recognition of its biological importance and its beneficial effects, the mechanism of H_2S action and the regulation of its tissue levels remain unclear in part owing to its chemical and physical properties that render handling and analysis challenging. Furthermore, the multitude of potential H_2S effects has made it difficult to dissect its signaling mechanism and to identify specific targets. In this review, we focus on H_2S metabolism and provide an overview of the recent literature that sheds some light on its mechanism of action in cellular redox signaling in health and disease. This article is part of a Special Issue entitled: Thiol-Based Redox Processes.

Keywords

Redox; Thiol; Hydrogen sulfide

1. Introduction

Sulfur-based chemistry is exploited by nature for maintaining cellular redox homeostasis, for redox-based signaling and for neutralizing reactive oxygen and nitrogen species. Reactive cysteine residues in the proteome are important constituents of redox signaling pathways. Reversible changes in the oxidation state of cysteines allow them to function as redox switches in multiple signaling pathways [1] and these residues are often targets of modifications. Additionally, transition metal centers with sulfur ligands can participate in redox-signaling pathways and function as biological redox sensors. Some key messengers used for communication through these redox hotspots are reactive oxygen species (ROS) and reactive nitrogen species (RNS) along with the gaseous signaling molecules such as CO, NO and H_2S. Recognition of H_2S as a signaling molecule in mammals took longer than NO and CO perhaps due to its long reputation as an environmental toxin and the prevailing view

☆This article is part of a Special Issue entitled: Thiol-Based Redox Processes.

☆☆This work was supported in part by a grant from the National Institutes of Health (HL58984 to R.B.) and the American Heart Association (13SDG17070096 to O.K.).

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that it was primarily relevant to microbial metabolism. However, since the first report of a physiological role for endogenously produced H_2S in mammals [2], there has been an explosion in the literature of its varied biological effects (Fig. 1). Among the signaling mechanisms invoked for H_2S, cysteine persulfidation is the one that is most commonly cited [3]. However, the technical problems associated with existing methods for the detection of proteomic persulfidation raise concerns about the validity of the identified targets [4] in addition to raising questions about how target specificity is achieved. The chemical versatility of H_2S and the multiplicity of its reported targets suggest that additional mechanisms might be involved in H_2S signaling.

Fundamental gaps in our understanding of how intracellular H_2S is regulated hamper in turn, our understanding of its mechanism of action and target selectivity. At least three enzymes, cystathionine β-synthase (CBS), cystathione γ-lyase (CSE) [5,6], and 3-mercaptopyruvate sulfurtransferase (MST) [7,8], contribute to H_2S production (Fig. 2a). Housekeeping enzymes produce H_2S and it is not known whether signaling by H_2S as with NO and CO, can be regulated by increased enzymatic synthesis. It is also not known how H_2S biogenesis is selectively regulated relative to the canonical transsulfuration reactions catalyzed by CBS and CSE [9,10]. The low tissue concentration of H_2S is a product of both the H_2S biogenesis and oxidation fluxes [11].

2. Tissue H_2S metabolism

2.1. H_2S production

H_2S is produced endogenously from cysteine and homocysteine via various reactions catalyzed by CBS and CSE [5,6] and from 3-mercaptopyruvate in a reaction catalyzed by MST [7,8] (Fig. 2a). 3-Mercaptopyruvate is derived via a transamination reaction between cysteine and α-ketoglutarate catalyzed by cysteine aminotransferase (CAT), which is identical to aspartate aminotransferase [12]. MST catalyzes the desulfuration of 3-mercaptopyruvate generating an MST-bound persulfide at an active site cysteine (C_{248} in the human sequence) and pyruvate [13,14]. The resulting persulfide on MST can be released as H_2S in the presence of a reductant. Thioredoxin is the most efficient of the thiophilic acceptors tested for MST and generates H_2S in the presence of thioredoxin reductase and NADPH [14,15].

While CBS, CSE and MST catalyze H_2S production efficiently at saturating substrate concentrations, their respective tissue distribution, expression levels and efficiency of H_2S generation at physiologically relevant substrate concentrations govern their relative intracellular importance to H_2S production. Based on murine tissue-specific expression studies of the transsulfuration enzymes, CBS appears to represent the major source of H_2S in the murine brain and kidney while CSE is primarily responsible for H_2S production in the liver [16]. This is consistent with other reports that CSE is the major source of H_2S in the liver and in peripheral tissues while its contribution in the brain is negligible [17,18]. Brain H_2S levels are essentially unaffected in the CSE knockout mouse despite a significant decrease in serum H_2S and decreased rates of H_2S production in the aorta and heart, consistent with the importance of CSE as a source of H_2S in peripheral tissues [18]. MST is expressed in the kidney, liver, aorta, and brain [19] and is apparently important for H_2S

production in the brain [20] and in the vasculature [8]. A detailed kinetic characterization of human MST has been reported recently [14]. The tissue concentrations and contribution of MST to endogenous H_2S production in comparison to CBS and CSE await elucidation. The kinetics of H_2S generation by CBS, CSE and MST are the subject of several recent reviews and are not covered here [21–23].

The biochemical mechanisms for rapidly modulating H_2S levels to induce or ablate H_2S-based signaling await elucidation. In addition to H_2S production, the transsulfuration pathway enzymes are responsible for the synthesis of cysteine from homocysteine, two substrates used for H_2S synthesis (Fig. 2a). Cysteine biogenesis by the transsulfuration pathway supplies a significant portion of cysteine needed intracellularly [9,10]. Although cysteine concentration is 90–100 μM in most tissues [24], pool sizes of metabolites derived from it, i.e. glutathione (~10 mM) and taurine (~20 mM) are high [24–27]. Partitioning of cysteine between multiple metabolic fates is highly regulated [28]. Mechanisms for diverting the transsulfuration enzymes to H_2S versus cysteine synthesis remain to be elucidated. Mutations at two conserved residues, Thr_{257} and Thr_{260} in human CBS differentially affect the canonical (homocysteine + serine $\rightarrow$ cystathionine + H_2O) versus H_2S producing (homocysteine + cysteine $\rightarrow$ cystathionine + H_2S) activities [29]. The Thr257Val mutation results in a ~10-fold decrease in the canonical activity while the H_2S generating activity is essentially unaffected. In contrast, introducing Ile at the same position decreases H_2S generating activity ~10-fold compared to a ~30-fold decrease in the canonical activity. These results suggest the possibility of independent regulation of H_2S generating versus the canonical activities of CBS [29]. The expression levels and activities of CBS and CSE are regulated in multiple ways (reviewed in [22]).

2.2. H_2S oxidation

Contrary to the widely varying reports in the literature, tissue H_2S is in the low 10–30 nM concentration range [11,30,31] with the exception of aorta, where the concentration is ~20–100-fold higher [32]. The flux of sulfur into H_2S in murine liver is comparable to that of glutathione, which is present at steady-state concentrations of 6–10 mM. Hence, the sulfide clearance rate must be high to account for the low steady-state H_2S concentrations [11]. Indeed, mammalian tissues harbor a high capacity for H_2S oxidation [33,34], which occurs in the mitochondria [35,36]. The oxidation products include persulfide, sulfite, thiosulfate $(S_2O_3^{2-})$ and sulfate (SO_4^{2-}). Sulfate constitutes ~90% of total urinary sulfur [37].

The structures and reaction mechanisms of enzymes involved in sulfide oxidation have been discussed in a recent review [23] and only an overview is presented here. The first step of H_2S oxidation is catalyzed by a sulfide quinone oxidoreductase (SQR), a flavoprotein localized in the inner mitochondrial membrane (Fig. 2b). SQR catalyzes the two-electron oxidation of sulfide to persulfide and transfers the reducing equivalents to ubiquinone via FAD [38], thus linking H_2S oxidation to mitochondrial energy production [35]. The physiological acceptor of the sulfane sulfur bound to mammalian SQR is not known and sulfite is reported to be an efficient acceptor of human SQR under in vitro assay conditions [39] (Fig. 2b, *path* 1).

Persulfide dioxygenase (the product of the human *ethe*1 gene) is a non-heme iron protein and catalyzes the oxidation of persulfide to sulfide. Under in vitro assay conditions, glutathione persulfide (GSSH) serves as a substrate for the persulfide dioxygenase [36,40]. Alternatively, rhodanese can catalyze the transfer of the sulfane sulfur from GSSH to sulfite to form thiosulfate [36]. The sulfide oxidation circuitry as presented (Fig. 2b) raises prickly questions for which answers do not currently exist. First, if persulfide dioxygenase is the second enzyme in the sulfide oxidation pathway [36], then what is the proximal acceptor that carries the sulfane sulfur from SQR to GSH (Fig. 2b, *paths* 1 versus 2)? Human SQR reportedly cannot use GSH as a sulfane sulfur acceptor and sulfide is a poor acceptor, generating hydrogen disulfide, H_2S_2 [39]. The alternative proposal, that sulfite accepts sulfane sulfur from SQR [39], poses a logical conundrum since sulfite (in the +4 oxidation state) is more oxidized than persulfide (S^0 oxidation state) and therefore should be formed downstream in the sulfide oxidation pathway. Hence, an alternative source of sulfite that supports the activity of SQR is needed for the operation of this version of the sulfide oxidation pathway. An alternative route to sulfite does exist in the cysteine catabolic pathway (Fig. 2b) where it is generated by the consecutive actions of cysteine dioxygenase and a transaminase, which generate cysteine sulfinic acid and β-sulfinylpyruvate, respectively; the latter decomposes to give sulfite and pyruvate [41,42]. The contribution of this catabolic pathway to the sulfite pool is, however, expected to be significant only under conditions of excess cysteine, when cysteine dioxygenase is stabilized [43].

Utilization of sulfite by SQR to generate thiosulfate also appears to be at odds with the clinical data on patients with ETHE1 deficiency who exhibit: (a) elevated levels of H_2S and thiosulfate, and (b) greatly reduced levels of sulfite [40]. If the role of persulfide dioxygenase is to provide sulfite for SQR, then, the diminished sulfite level in ETHE1 deficiency could be explained by the inactivity of persulfide dioxygenase and possibly, by the exhaustion of a limited sulfite supply that is generated via the cysteine catabolic pathway. However, the increase in the product of the SQR reaction i.e. thiosulfate (Fig. 2b, *path* 1) and the substrate, H_2S, is difficult to explain. The existence of microbial variants in which persulfide dioxygenase and rhodanese are fused suggests utilization of the toxic product of the dioxygenase reaction, i.e. sulfite, by rhodanese. Clearly, a better understanding of the organization of the sulfide oxidation pathway is needed. Increased GSH synthesis by administration of the precursor, N-acetyl cysteine, is an effective treatment for ethylmalonic encephalopathy, caused by mutations in *ethe*1 and promotes clearance of high levels of H_2S by accepting SQR-borne persulfide forming GSSH [44]. These results are consistent with a role for GSH in the sulfide oxidation pathway.

2.3. Bound sulfane sulfur pool

In addition to free H_2S, acid labile and protein-bound sulfane sulfur represent two other sulfur pools that are potentially important in H_2S metabolism. The acid-labile sulfur pool is associated with iron–sulfur cluster-containing proteins, which are ubiquitous in cells and tissues [45]. Release of sulfide from this pool is unlikely to modulate endogenous H_2S levels and is expected to depend on protein turnover. Protein bound persulfides can be formed either by the transfer of a sulfane sulfur group from a protein-bound or small molecule donor to a cysteine acceptor (Fig. 3a,b) or by attack of sulfide on an oxidized cysteine (Fig. 3c–e).

H_2S can be released from persulfides in the presence of a reductant. The tissue content of cyanolyzable sulfur (i.e. of persulfides) is reported to be ~40, ~324, ~18 and ~34 nmol/g tissue in the rat liver, kidney, heart and spleen [17]. A significant pool of H_2S is reportedly stored as bound sulfane in the brain and ~1.5 μmol H_2S/g protein was released from mouse brain homogenate by DTT treatment [46]. Gomori-positive granules in periventricular astrocytes are postulated to contain sulfane sulfur [47]. Cyanide treatment decreased the number of these granules in the brain, while treatment with diallyl disulfide, an H_2S source, increased their number [48]. While the function of the cytoplasmic Gomori-positive inclusions is not known, their involvement in sulfane sulfur metabolism has been proposed [48]. The bound sulfane sulfur pool is proposed to be important for modulating H_2S levels in response to cellular demand [46]. Persulfides are chemically labile and it is not known how a sulfane sulfur pool, if one exists, is protected from continuously leaking H_2S in the reducing milieu of the cell.

3. Chemical properties of H_2S

H_2S is a weak acid and readily ionizes in aqueous solution with pK_{a1} and pK_{a2} values of 6.9 and > 12 respectively [49]. Therefore at physiological pH, approximately two thirds of total H_2S is in the anionic sulfide (HS^-) form. Further ionization to S^{2-} requires alkaline conditions. Hence, the concentration of the sulfide dianion is negligible under cellular conditions. H_2S is lipophilic and can freely diffuse through membranes [50]. While the electronic configuration of sulfur is similar to that of oxygen, their chemical properties are quite different. Sulfur is less electronegative than oxygen. The more diffuse orbital system and more polarized electron cloud of H_2S make it a better nucleophile compared to water at physiological pH. With six valence electrons and a vacant 3d orbital, sulfur can expand its valence shell to accommodate extra electrons resulting in oxidation states ranging from −2 to +6. Sulfane sulfur is in the S^0 oxidation state. It is labile and reactive and the terminal or sulfane sulfur atom can be transferred between thiophilic acceptors [51]. Examples of biologically important sulfane sulfur compounds include persulfide (RSSH), thiosulfate ($S_2O_3^{2-}$), hydropolysulfides (RS_nH), polysulfides (RS_nR, n > 2), polythionates ($^-SO_3 - S_n - SO_3^-$), and elemental sulfur (S_8) that can function in sulfide storage in cells [52].

The sulfur in H_2S is in the −2 oxidation state, which represents the most reduced form of sulfur. The two-electron redox potential of H_2S ($HS^- \rightarrow S^o + H^+ + 2e^-$) is +0.17 V at pH 7 [53], which makes it a weaker reductant than cysteine and glutathione. The cytoprotective role of H_2S has been attributed to its antioxidative capacity [54–58] and a direct role for H_2S in scavenging reactive oxygen/nitrogen species such as HOCl [59], ONOO– [60] and •NO [61,62] has been proposed. While the second order rate constant for the reaction of H_2S with HOCl, an inflammatory mediator in neutrophils, is large [63], the rate constants for its reaction with other biologically relevant oxidants is small [64,65] and would appear to argue against a significant antioxidant role. However, the products of these reactions, if formed, could be important for cellular function especially under oxidative stress conditions. For example, the two-electron oxidation of H_2S by H_2O_2 would yield sulfenic acid (HSOH), which can react with a second mole of H_2S to generate H_2S_2. Oxidation of H_2S by

peroxynitrite was reported to generate nitrite and H_2S_2 in one study [64] and thionitrate ($HSNO_2$) was present predominantly as sulfinyl nitrite (HS(O)NO) in another [65]. It was proposed that unlike thiols, H_2S reacts with peroxynitrite through an associative mechanism [65]. Sulfinyl nitrite can act as an •NO donor. One electron oxidation of H_2S by peroxynitrite-derived secondary radicals (e.g. $•NO_2$, HO•, $CO_3^{•-}$) yields a highly reactive sulfanyl radical ($S^{•-}$), which can initiate a radical chain reaction in the presence of oxygen forming a range of oxidation products [64]. In addition to its intrinsic ability to modify various cellular targets [66], $S^{•-}$ can react with oxygen to form $SO_2^{•-}$ or with HS^- to form $HSS^{•2-}$. Alternatively $S^{•-}$ can interact with a second mole of $S^{•-}$ to give H_2S_2 [64]. Other secondary radicals such as $SO_2^{•-}$ [64,67–69] and $SO_3^{•-}$ [70] have been detected using spin trapping experiments. Although the reported cytoprotective effects of H_2S are attributed in part to its reactivity towards various oxidant species, the relatively small rate constants for most H_2S oxidation reactions together with the low intracellular concentration of H_2S versus the more abundant reductants, e.g. glutathione and cysteine, makes a significant role for H_2S as an antioxidant scavenger unlikely.

H_2S can react with disulfides and oxidized thiols generating persulfide [71]. Persulfides are labile and unless sequestered, are susceptible to reduction or transsulfuration reactions with other acceptors. The sulfane sulfur atom in persulfides is nucleophilic [4]. Since the S–H bond in persulfides is ~22 kcal/mol weaker than the S–H bond in thiols [72], persulfides are stronger acids with p*K*a values that are ~1–2 units lower compared to the corresponding thiols [73,74]. Persulfide anions are more nucleophilic and better antioxidants than the corresponding thiolates [75] and perthiyl radicals are more stable than thiyl radicals [73]. Reaction of H_2S with nitrosothiols forms thionitrous acid (HSNO) adding a new player that might be involved in H_2S signaling [76]. Other reactions of H_2S involve its reactivity with transition metals and its ability to undergo nucleophilic addition and substitution reactions with unsaturated carbonyl compounds, nitrogen oxides and other biological electrophiles.

4. Mechanisms of H_2S-based signaling

4.1. Protein persulfidation

An increasing number of reports suggest the importance of protein persulfidation in H_2S-based signaling [77]. In principle, persulfidation can occur by one of at least three mechanisms: (i) nucleophilic attack of a sulfide anion on an oxidized cysteine residue, e.g. sulfenic acid, S-nitrosyl or disulfide, (ii) via transsulfuration from an existing persulfide carried by a small molecule like GSSH or a protein, or (iii) by attack of a cysteine thiol on H_2S_2 [78] (Fig. 2a,b) or polysulfide [79]. While the inherent lability of the persulfide modification and the lack of obvious mechanisms for achieving target specificity are issues that need to be addressed for establishing persulfidation as a significant mechanism of sulfide-based signaling, examples of persulfidation influencing enzyme activity have been around in the literature for over four decades [80–82]. Although protein sulfhydration was reported to be as prevalent as phosphorylation [77], the inability of the modified biotin switch assay used in this study, to distinguish between persulfides and other sulfur species, especially thiols [4], raises questions about the reported 10–25% prevalence of persulfidation in the liver proteome and the specific proteins that were identified [77].

Assessing the importance of the persulfide modification for H_2S signaling and its prevalence in the proteome, await development and application of persulfide-selective reagents together with the direct identification of the persulfide modification by mass spectrometry.

Persulfidation of the active site cysteine in protein tyrosine phosphatase, PTP1B, was demonstrated by mass spectrometry both with purified protein and under cell culture conditions [83]. Persulfidation inactivates PTP1B and leads to accumulation of phosphorylated PERK in response to ER stress. Persulfidation of the p65 subunit of NF-κB in response to TNFα treatment, demonstrated by LC-MS/MS, increases its antiapoptotic function and is dependent on CSE expression [84]. DNA binding of NF-κB and transcriptional activation of antiapoptotic genes was decreased in CSE knockout mice [84]. The modified cysteine in p65 is also a target for S-nitrosylation, which has the opposite functional consequence [84]. Persulfidation of ATP-sensitive K^+ channels reportedly elicits channel opening and results in hyperpolarization of endothelial smooth muscle cells and vasodilation, which is impaired in CSE knockout mice [85,86].

4.2. Interaction of H_2S with S-nitrosothiols

Accumulating evidence for the interaction between •NO and H_2S signaling pathways provides a new perspective for potentially understanding the mechanism of H_2S action. H_2S and •NO show some synergistic physiological effects indicating cross talk between the two signaling systems [87–93]. A molecular mechanism for the interaction between the H_2S and •NO signaling pathways is suggested by the identification of nitrosothiol (HSNO) formed by the reaction of H_2S and •NO donor compounds in vitro [61]. H_2S treatment blocked •NO release from various •NO donor compounds and blocked •NO-dependent increase in cGMP levels in cell culture. Formation of nitrosothiol was inferred by EPR spectroscopy, amperometry and nitrite measurement and the effect on cGMP levels was reversed by Cu^{2+} consistent with the formation of an adduct between H_2S and •NO species [61]. HSNO is also formed by the reaction of H_2S with S-nitrosothiols, e.g. GSNO, suggesting a physiologically relevant alternative mechanism for its formation [76] (Fig. 4). In principle, HSNO can generate NO^+, NO•, NO^- and HNO potentially eliciting diverse specificities and physiological functions [76]. Since HSNO can freely diffuse across membranes [50], it can potentially be used to transnitrosylate proteins at sites remote from the site of •NO synthesis. Despite its known cardioprotective role [94–98], the physiological relevance of HNO as a signaling molecule has been open to question. Formation of HNO in endothelial cells has been demonstrated using a nitroxyl sensitive fluorescence probe [76]. The formation of HNO in a direct displacement reaction of GSNO by GSH had been previously proposed [99,100]. In these studies, nitrous oxide (N_2O) and hydroxylamine were used as markers for HNO formation since N_2O is generated by decomposition of the HNO dimerization product, hyponitrous acid [100,101].

High-level ab initio calculations indicate that the RSNO wave function possesses significant multireference character [102,103] due to its zwitterionic RS^+/NO^- structure. Nucleophilic attack on the sulfur atom in the ion pair by a thiolate would yield HNO. By analogy, a nucleophilic attack on the sulfur atom of RSNO by HS^- would produce HNO and H_2S_2. Similarly, an attack by a thiolate would produce a persulfide, representing an alternative

route to persulfide formation. It has been proposed that HNO mediates at least some of the pharmacological effects of sodium nitroprusside ($Na_2[Fe(CN)_5(NO)]$), a potent vasodilator [93,104]. Nitrosylation of thiols [105] and modulation of voltage-dependent K^+ channels [106] by HNO have been reported. Importantly, the effect of Angeli's salt, an HNO donor, on myocyte contractility mimics the effect of treatment with sodium nitroprusside and H_2S [93].

4.3. Sulfhydration of electrophiles by sulfide

Recently, direct sulfhydration of various cellular electrophilic messengers, such as 8-nitro-cGMP, nitro- and keto- derivatives of unsaturated fatty acids and cyclopentenone prostaglandin, by sulfide has been reported and provides an additional mechanism for H_2S-mediated signaling (Fig. 5) [107]. Electrophiles are generated endogenously as byproducts of oxidation reactions and also as byproducts of lipid peroxidation reactions in the presence of ROS and RNS species and primarily react with cysteine residues to initiate signaling [108–111]. S-alkylation of cysteine sulfhydryl groups by electrophilic metabolites such as 8-nitroguanosine 3′,5′-cyclic monophosphate and cyclopentenone prostaglandins and isoprostanes [109,112] mediates various redox-dependent signaling pathways [108] including cGMP-dependent NO signaling [113]. H_2S treatment blocks iNOS-dependent S-guanylation (i.e. formation of a cysteine-cGMP adduct) of H-Ras, a modification that activates H-Ras to signal cell senescence in response to stress [107]. The protective role of H_2S in myocardial infarction-associated heart failure was proposed to be due in part to increased levels of 8-SH-cGMP and the concomitant loss of H-Ras activation. Protein S-guanylation level was increased by CBS knockdown in various human cell lines [107]. S-guanylation of H-Ras is an example of a system where H_2S and •NO elicit opposing functions. Covalent modification of a cysteine in the p50 subunit of NF-κB by 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d–PGJ2), inhibits DNA binding [114], which can be protected by sulfhydration of 15d–PGJ2 [107]. Sulfhydration of the p65 subunit of NF-κB induces its antiapoptotic functions [84]. 15d–PGJ2 also suppresses angiogenesis [115,116]. These findings indicate that H_2S could modulate •NO based signaling either via transnitrosylation or competition with targets of •NO. Synergistic effects of H_2S and •NO in the endothelial system, where both induce vasorelaxation, might be due to transnitrosylation mediated by H_2S.

4.4. Interaction of H_2S with metal centers

Another potential mechanism for H_2S-dependent signaling is its interaction with metal centers. H_2S can either reduce the metal center or it can coordinate to it depending on the stereoelectronic characteristics of metal-containing active site. With hemeproteins, polar active sites and high H_2S concentrations promote heme reduction by H_2S where as non-polar active sites promote formation of a heme–H_2S complex (Fig. 6) [117]. With a stronger nucleophilic character, compared to water, sulfide can easily displace water that generally fills empty coordination sites at metal centers in the active sites of proteins. H_2S binds to both heme a_3 and Cu_B in the binuclear center [118] and reversibly inhibits cytochrome c oxidase, which results in a drop in the metabolic rate inducing a state of suspended animation [119]. The K_i for sulfide inhibition is 0.2 μM and ~20 μM with purified cytochrome c oxidase [120] and in intact cells [121], respectively. Isolated mitochondria

respire maximally in the presence of 10 μM H_2S consuming oxygen and generating ATP but the rate decreases with increasing sulfide concentrations due to inhibition of cytochrome c oxidase [122]. Decreased ROS generation is one consequence of inhibition of cytochrome c oxidase by H_2S, which is believed to account for the protective effect of H_2S donors in reperfusion-associated cardiac injury.

Invertebrates living in sulfide-rich habitats use hemoglobin to transport sulfide to symbiotic bacteria to protect themselves from H_2S toxicity [46]. The mollusk, *Lucina pectinata*, which lives in sulfide-rich mangroves, uses ferric heme to transport H_2S. Although it possesses three types of hemoglobin, only hemoglobin I binds H_2S [46]. The reactivity of H_2S with mammalian hemoglobin and myoglobin varies and is partly determined by the organization of the active site [117]. It is not known whether and if, coordination or reduction of metal centers by H_2S is involved in signaling. H_2S can react with ferric hemoglobin to form sulfhemoglobin, which might function as a metabolic sink for H_2S under some conditions [123].

5. Cellular and physiological processes regulated by H_2S

5.1. Vasorelaxation

H_2S functions as an endothelial-derived hyperpolarizing factor (EDHF) and its vasorelaxant activity is ascribed primarily to activation of K_{ATP} channels [18,62,85–87,124]. The effect of H_2S on relaxation of blood vessels is sensitive to the presence of K_{ATP} channel inhibitors and believed to involve direct channel activation by H_2S [85,86,124,125]. Alternatively, an indirect mechanism can be considered as inhibition of cytochrome c oxidase results in reduced ATP levels, which activate K_{ATP} channels [126]. H_2S-induced vasorelaxation is independent of the cGMP-mediated pathway. Hyperpolarization by acetylcholine, which is mediated by intermediate- and small-conductance potassium channels, is dependent on CSE expression [86]. CSE knockout mice suffer from hypertension, exhibit endothelial dysfunction and are deficient in inducing endothelial-dependent hyperpolarization, consistent with H_2S functioning as an EDHF [18,86]. While $CSE^{-/-}$ mice exhibit decreased H_2S levels (~80% lower in the heart and aorta and 50% lower in the serum), they have significantly increased plasma homocysteine and reduced glutathione levels in the aorta and mesenteric artery beds [18], which could also contribute to the observed endothelial dysfunction in these animals [127].

5.2. Neuromodulation

H_2S functions as a signaling molecule in the brain and facilitates long-term potentiation in hippocampal neurons by activating NMDA receptors [2] and activates Ca^{2+} channels increasing Ca^{2+} influx into glial cells [128]. In addition to signaling, several lines of evidence indicate a neuroprotective role for H_2S. Opening of K_{ATP} channels by H_2S protects hippocampal pyramidal neurons from excitotoxicity and cell death [55] and K^+ channel openers are considered to have therapeutic potential for diseases such as epilepsy [129]. Upon exposure to high levels of the neurotransmitter, glutamate, H_2S is reported to increase neuronal antioxidant capacity by enhancing intracellular glutathione as a consequence of increasing uptake of cystine and cysteine and activating γ-glutamylcysteine synthase [54].

H_2S also protects immortalized mouse hippocampal cells from oxidative glutamate toxicity and in addition to increasing glutathione synthesis, activates K_{ATP} and Cl^- channels [55]. However the mechanism by which H_2S modulates the cystine/glutamate antiporter to increase intracellular cysteine at high extracellular glutamate concentrations is not known. Increased synthesis and redistribution of glutathione to mitochondria is proposed to protect neuronal cells from oxidative stress induced by H_2O_2 [130]. Overexpression of mitochondrial MST and CAT protects cells from glutamate toxicity suggesting an anti-oxidative role for endogenously produced H_2S [130]. Involvement of H_2S in neuronal cell differentiation has been reported recently [131]. Cysteine supplementation induced proliferation and differentiation of neuronal stem cells to neurons and astroglia, which was attenuated by siRNA-induced inhibition of CBS expression [131].

5.3. Regulation of ion channels

Ion channel regulation is believed to be an important mechanism for mediating the physiological effects of H_2S [132,133]. K_{ATP} channels are widely distributed in mitochondrial and plasma membranes and their modulation by H_2S is reportedly important for myocardial protection against ischemia/reperfusion injury [134], insulin secretion by pancreatic β-cells [135], protection against glutamate induced neuronal toxicity [55] and regulation of nociception [136] and inflammation [137]. H_2S activates K_{ATP} channels and brings about relaxation of endothelial smooth muscle cells [85]. Activation of the K_{ATP} channel apparently occurs by persulfidation at Cys_{43} in the pore-forming Kir6.1 subunit [86], which decreases ATP binding and promotes channel binding to phospholipid phosphatidylinositol 4,5-bisphosphate. Mutations at Cys_6 and Cys_{105} in the extracellular loop of the regulatory SUR1 subunit of the rat K_{ATP} channel, also impaired H_2S-dependent activation suggesting their involvement in H_2S-modulation of channel function [138].

H_2S has also been implicated as a modulator of other channels including the Ca^{2+}-sensitive K^+ channel (BK_{Ca}), L-type and T-type Ca^{2+} channels, chloride channels, members of the TRP (transient receptor potential) family of channels and Na^+ channels (reviewed in [133]). Of these, regulation by H_2S of the BK_{Ca}, important for oxygen sensing, is particularly interesting, since H_2S also functions as an oxygen sensor [139,140]. Studies with glomus cells from the rat carotid body and of human channel proteins expressed in HEK293 cells suggested an inhibitory role for H_2S with high IC_{50} values: 670 μM [141] and 275 μM [142]. However, conflicting results have also been reported with H_2S activating rather than inhibiting BK_{Ca} channels in rat pituitary tumor cells albeit with high EC_{50} values (169 μM and 2 mM in a biphasic dose dependence response) [143].

H_2S regulates low-voltage activated T-type Ca^{2+} channels, which are responsible for the pacemaker potential in the heart and low-threshold spikes in the central nervous system. H_2S increases T-type Ca^{2+} channel currents in mouse N18TG2 neuroblastoma cells [144]. These channels are involved in epilepsy and chronic pain [145,146]. High voltage L-type Ca^{2+} channels from rat cerebellar granule neurons are also reportedly activated by H_2S. However, cardiac myocyte L-type Ca^{2+} channels isolated from both spontaneously hypertensive rats and normal rats are reportedly inactivated by H_2S [147–149] suggesting tissue/cell specific regulation. Activation of Na^+ channels has also been reported by addition of NaSH by a

mechanism proposed to be sensitive to reducing agents [133,150] and alkylating agents [133,150] suggesting involvement of cysteine modification. Activation of the TRP family of channels, TRPV1 and TRPA1, is proposed to stimulate neukinin-mediated neurogenic inflammation response and increases intracellular Ca^{2+} [133,151,152]. Conversely, H_2S inhibits chloride channels by decreasing the open probability of the channel [55,133,153,154]. It is important to note however that high concentrations of H_2S (up to 1 mM) were used in many of these studies.

5.4. Endoplasmic reticulum (ER) stress

Stresses such as infection, inflammation, and increased synthesis of secreted proteins such as in diabetes or conditions triggering abnormal folding of proteins can result in accumulation of misfolded or unfolded proteins leading to compromised ER function and induction of the unfolded protein response. The latter activates autophosphorylation of an ER resident kinase, PERK, which in turn phosphorylates eukaryotic initiator factor 2α resulting in inhibition of general protein synthesis providing a temporal window for reestablishment of cellular homeostasis. Persulfidation of PTP1B, a tyrosine phosphatase that dephosphorylates PERK, at the active site cysteine is seen in response to ER stress and is dependent on CSE activity [83]. Persulfidation of PTP1B inhibits its activity resulting in higher level of PERK phosphorylation under ER stress conditions. Consistent with these results, CSE expression increases in response to ER stress by a mechanism dependent on ATF4 (activating transcription factor 4) [155], a transcription factor that is activated in response to ER stress. Disruption of the ATF4 gene results in decreased CSE expression and concomitant decrease in cellular glutathione levels. $CSE^{-/-}$ mouse embryonic fibroblast cells are susceptible to ER stress-induced cell death [155]. Together, these results suggest a regulatory role for H_2S in the ER stress response.

5.5. Hypoxia

The carotid body is important for oxygen chemoreception and in response to reduced O_2 partial pressure, signals to the central nervous system, which initiates an autonomic reflex leading to increased respiratory rate and activation of the sympathetic nervous system, which in turn leads to vasoconstriction resulting in increased blood pressure and heart rate. However, the mechanism by which O_2 tension is sensed is not well understood. Carotid body activity is inhibited under normoxia by CO and NO [156]. It has been hypothesized that H_2S metabolism is involved in oxygen sensing since hypoxic conditions lead to increased intracellular H_2S due to decreased mitochondrial H_2S oxidation [157]. H_2S treatment of isolated pulmonary arteries produces contractile patterns similar to that induced by hypoxia [157] and in perfused trout gills [158]. H_2S administration to specialized chemoreceptor organs of trout resulted in a dose-dependent reduction of heart rate and an increase in ventillatory frequency mimicking hypoxia [139]. Removal of the first pair of gills that contains chemoreceptors analogous to the vertebrate carotid body, inhibited H_2S-induced reduction in heart rate consistent with a role for H_2S in O_2 sensing in this organ [139]. A concentration-dependent activation of murine afferent nerves in the carotid body was observed in response to NaHS [140]. Activation of chemoreceptor afferent nerve by hypoxia was decreased by inhibition of CBS but not CSE. As seen with hypoxia, NaHS inhibited BK_{Ca} channel currents and the inhibition was alleviated by a CBS inhibitor [140].

CSE deficiency induced pharmacologically or achieved via gene disruption in mice impaired carotid body response to hypoxia [159]. NaHS has been shown to inhibit BK_{Ca} channel activity by decreasing the open state probability, albeit with a very high IC_{50} value as discussed above (275–670 μM) [141,142]. The mechanism and physiological relevance of BK_{Ca} channel modulation by H_2S remain to be elucidated.

5.6. Inflammation

Inflammation is a complex process orchestrated by a proinflammatory phase characterized by activation and trafficking of lymphocytes and macrophages to the affected area and expression of pro-inflammatory cytokines followed by a resolution phase characterized by secretion of anti-inflammatory mediators and induction of apoptosis of infiltrating lymphocytes leading to clearance of the affected area. Dysregulation in this process could lead to chronic inflammation. A growing number of reports implicate a regulatory role for H_2S in inflammatory processes although mechanistic insights are limited and both pro- and anti-inflammatory effects of H_2S have been reported.

H_2S treatment reduced leukocyte adherence to rat mesenteric venules, which was reversed by a $K(_{ATP})$ channel blocker or inhibition of CSE [160]. H_2S also prevented infiltration of neutrophils and lymphocytes into endothelial walls [160,161], reduced expression of pro-inflammatory cytokines IL-1B, IL-6, TNFα, and prostaglandin E [162,163], and attenuated mucosal injury [164]. Intraperitoneal administration on NaHS in an oleic acid-induced acute lung injury model in rat resulted in decreased expression of the pro-inflammatory cytokines IL-6 and IL-8 and increased levels of the anti-inflammatory cytokine, IL-10 [165].

Oxidized products of LDL, implicated in the inflammatory response, decreased CSE expression and H_2S production in macrophages [166]. CSE overexpression in the transformed macrophage cell line, Raw264.7, and in primary macrophages blocked the oxidized LDL-induced increase in TNFα level and subsequent NF-κB activation while CSE knockdown elicited the opposite effect [166]. A negative correlation between blood H_2S level and the LDL: HDL ratio has been reported, which could be explained by a positive correlation between H_2S and HDL [167]. Inhibition of H_2S synthesis resulted in inflammation and colonic mucosal injury in healthy rats, decreased cyclooxygenase-2 (COX-2) expression and reduced prostaglandin E2 production [168]. COX-2 generates anti-inflammatory electrophilic oxo-derivatives of fatty acid [169] while prostaglandin E2 inhibits expression of inflammatory chemokines [170] and production of TNFα [171]. H_2S induced polymorphonuclear cell apoptosis, consistent with promoting an inflammatory response during the resolution phase [172]. The high H_2S concentration used in this study (1 mM) was explained as being relevant to anaerobic infections such as in chronic periodontitis, frequently associated with microflora that are sulfide-producing [172].

On the other hand, studies suggesting that H_2S is a proinflammatory agent, which increases production of pro-inflammatory cytokines [173] and modulates leukocyte trafficking (i.e. rolling and adhesion), have been reported [174,175]. H_2S levels increase in LPS-induced rodent models of systemic inflammation and inhibition of H_2S production was reported to be protective [174,176–178]. Increased CSE [176,178] and CBS [178] expression was correlated with inflammation in these studies. Inhibition of CSE-dependent H_2S synthesis

decreased carrageenan-induced paw edema in mouse [179] and increased plasma H_2S was seen in rats exposed to hemorrhagic shock [180]. Patients with septic shock [176] or various types of shock [181] displayed increased plasma H_2S. The discrepancy in the literature on the effect of H_2S in inflammation could be due to the phase of the inflammation that was characterized or alternatively, the varying and often relatively high, concentrations of H_2S used [162]. High bolus concentrations of NaHS produce a burst of H_2S in a short period of time that may not be physiologically relevant.

5.7. Role of H_2S in mitochondrial bioenergetics

The ability to oxidize H_2S is an ancient one inherited from prokaryotes that utilize sulfur compounds such as sulfide as electron donors to generate energy. Invertebrates such as clams and worms living in sulfide-rich environments also use sulfide as an inorganic energy source coupling its oxidation to mitochondrial oxidative phosphorylation [35,182]. At higher concentrations, i.e. >20 μM, cytochrome c oxidase is inhibited in intact cells and H_2S acts as a poison for the electron transfer chain [126]. Efficient oxidation of sulfide is important for averting its buildup and consequent toxicity [183]. Sulfide oxidation is activated at concentrations as low as 10–20 nM, helping maintain subtoxic concentrations of H_2S [184]. Studies on isolated mitochondria and murine hepatoma cells revealed that low concentrations (0.1–1 μM) increase while higher concentrations (3–30 μM) inhibit respiration [185]. The presence of 10–100 nM 3-mercaptopyruvate enhanced mitochondrial electron transport activity, which was reversed by suppression of MST or SQR expression suggesting the potential role for sulfide metabolism in regulating cellular energetics [185].

Reversible inhibition of cytochrome c oxidase decreases metabolic rate [119] and mediates the cytoprotective effects of H_2S during myocardial ischemia reperfusion by decreasing production of damaging ROS [186]. It is not known whether and how mitochondrial sulfide metabolism is regulated in response to cellular needs for H_2S. The quantitative significance of mitochondrial sulfide oxidation to ATP production also awaits elucidation.

5.8. Apoptosis

Overexpression of CSE in human smooth muscle cells results in significant inhibition of cell growth and in increased apoptosis, which are proposed to be due to an increased endogenous production of H_2S [187]. These cells also exhibit increased extracellular signal-regulated kinase (ERK) and MAP kinase activation, induction of p21 and down-regulation of cyclin D1 expression [187]. Smooth muscle cells derived from CSE knockout mice showed enhanced proliferation compared to cells derived from wild-type mice [188]. $CSE^{-/-}$ cells were more susceptible to H_2S-induced apoptosis than control cells and displayed decreased phosphorylation of ERK in mesenteric arteries [188]. Exogenously added H_2S or overexpression of CSE reduced viability of insulin-secreting pancreatic beta cells [189] and decreased insulin secretion [135]. The effect of H_2S on cell fate could be cell-type specific. For example, pancreatic beta cells specialized to express and export high concentrations of insulin, could be sensitive to H_2S-mediated modulation of their highly regulated ER function.

Anti-apoptotic effects have also been reported for H_2S. Human neuroblastoma SH-SY5Y cells were protected by H_2S from 6-hydroxydopamine-induced injury [190] and PC12 cells were protected by H_2S against methyl phenylpyridinium-induced cytotoxicity and cell death [191]. H_2S protected cells from oxidative glutamate toxicity by stimulating production of glutathione [54,130,192]. The anti-apoptotic action of NF-κB is mediated by H_2S-dependent persulfidation and is markedly diminished in CSE knockout mice [84]. Further studies are needed to elucidate the opposing pro- and anti-apoptotic effects of H_2S.

5.9. Gastrointestinal physiology

H_2S is proposed to play a regulatory role in the gastrointestinal tract by modulating intestinal contractility [193], by affecting colonic ion secretion via involvement of potassium channels [194,195] and by its excitatory action on enteric neuorons [196–198]. Intestinal microflora produces large amounts of H_2S by degradation of sulfur-containing organic compounds and by dissimilatory sulfate reduction. Consequently, H_2S can reach up to millimolar concentrations [199] and its levels correlate with the dietary protein intake [200]. A significant proportion of intestinal H_2S is bound to fecal components and the free H_2S content is low [199]. The colonic mucosa has a high capacity for oxidizing sulfide to thiosulfate [201,202], which is accompanied by mitochondrial energization [183], thus protecting against the injurious effects of high sulfide levels. The cecal and colonic mucosa also express high thiol methyltransferase activity, which can generate methanethiol [203] and high steady-state levels of rhodanese are found in the submucosa and crypts of the colon [204].

Imbalance in colonic epithelial cell sulfide oxidation is proposed to be a contributing factor in the pathogenesis of ulcerative colitis, an inflammatory bowel disease characterized by epithelial cell damage [205]. Excess H_2S is proposed to inhibit oxidation of butyrate [206], a major energy source for colonic epithelial cells [207]. Inhibition of butyrate utilization could exacerbate cell damage leading to inflammation of colonic crypts. Fecal H_2S production is increased in patients with ulcerative colitis [208] although the fecal count of sulfate reducing bacteria in controls versus ulcerative colitis patients was not found to differ [209]. Sulfide oxidation was reportedly ~3-fold lower at sites of mucosal ulceration in hapten-induced colitis in rats versus in healthy controls while H_2S production was increased and mirrored in enhanced expression of CSE and MST (10- and 3-fold respectively), and diminished expression of SQR (~3-fold) [210]. Rhodanese expression and activity were diminished in colonic tissues in dextran sulfate sodium-induced colitis in mice, consistent with a role for impaired sulfide clearance in inflammatory bowel disease [211]. Administration of high concentrations of methionine or S-adenosylmethionine 1,4 butane disulfonate to rat colonocytes ablated the effects of sulfide toxicity and was proposed to be due to sulfide methylation [212].

The role of H_2S in ulcerative colitis is however controversial. No detectable difference in colonic luminal sulfide levels between ulcerative colitis and control subjects has been reported [213]. In dextran sulfate-induced ulcerative colitis in rats, administration of a sulfide binding compound, bismuth subsalicylate, reduced fecal sulfide release but did not protect against colitis, indicating that elevated sulfide does not play a role in the etiology of

colitis, at least in this model [214]. On the other hand, other studies have reported a protective role for H_2S in healing of gastric ulcers and colitis [215,216], gastric injury caused by anti-inflammatory nonsteroidal drugs [164] and resolution of colitis [168]. It is important to note that experimental models of ulcerative colitis might be substantially different from the naturally occurring disease and the effect of H_2S could be dependent on both the experimental model as well as the stage of colitis.

6. Summary

As fast-moving as the field of H_2S biochemistry has become, the pace is tempered by the many gaps in our understanding of the molecular mechanisms underlying sulfide oxidation, H_2S homeostasis and H_2S signaling targets. These gaps in knowledge also represent opportunities for moving the field forward. The controversies surrounding the sometimes dichotomous effects of H_2S (e.g. it is both pro- and anti-inflammatory) highlight the problems associated with interpreting studies performed with a wide concentration range of H_2S and the technical challenges with handling a redox-active gas. Given the profound physiological effects attributed to H_2S, it is expected that it will continue to enjoy attention particularly in the areas of redox-signaling mechanisms and the enzymology of its biogenesis and decay in the context of health and disease.

Abbreviations

AdoMet	S-adenosylmethionine
AdoHcy	S-adenosylhomocysteine
ATF4	activating transcription factor 4
BK_{Ca}	large conductance calcium-sensitive potassium channel
CBS	cystathionine β-synthase
COX-2	cyclooxygenase-2
EDHF	endothelial-derived hyperpolarizing factor
ER	endolasmic reticulum
ERK	extracellular signal-regulated kinase
ETHE1	persulfide dioxygenase
GSH	glutathione
H_2S	hydrogen sulfide
ROS	reactive oxygen species
RNS	reactive nitrogen species

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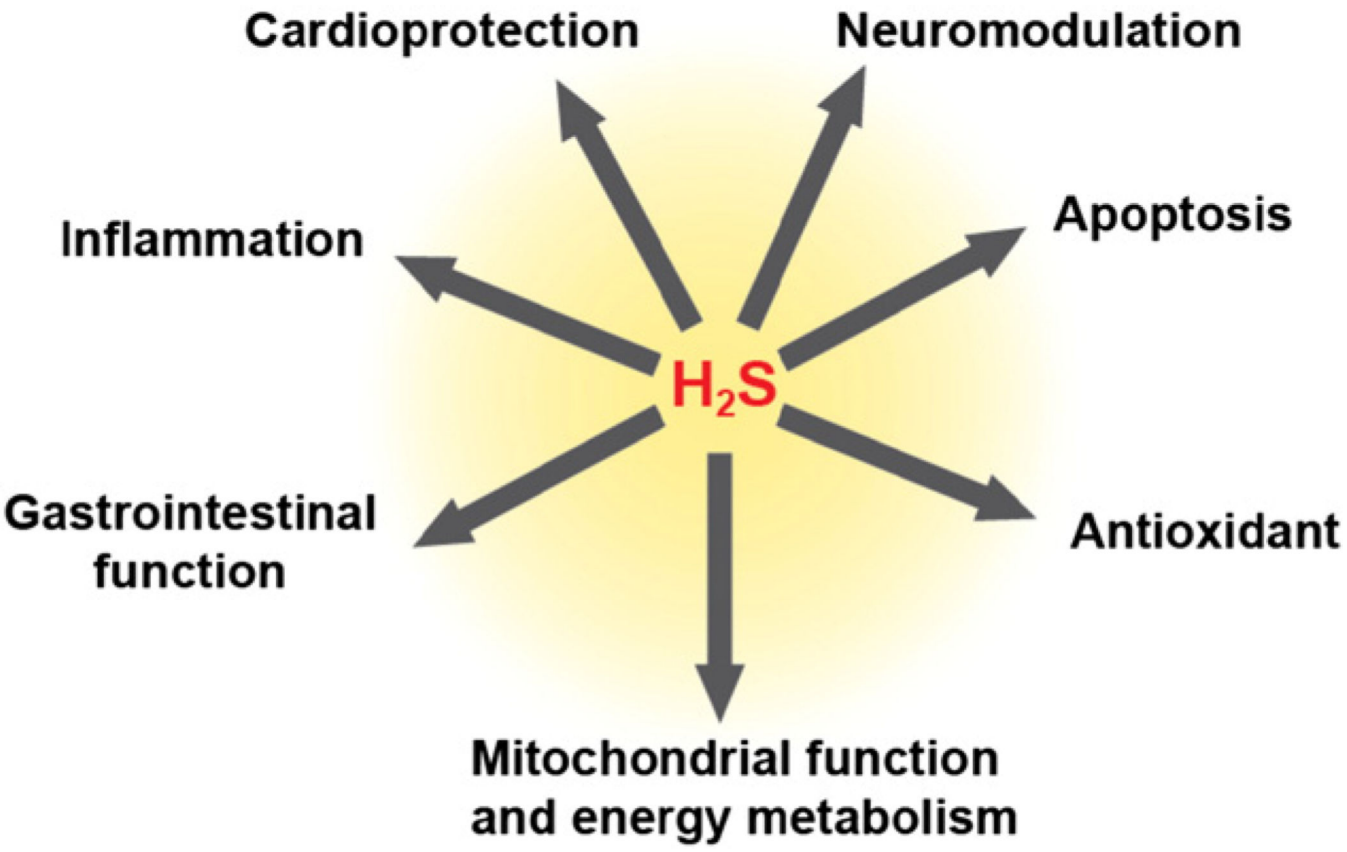

Fig. 1.
Overview of the physiological effects elicited by H_2S.

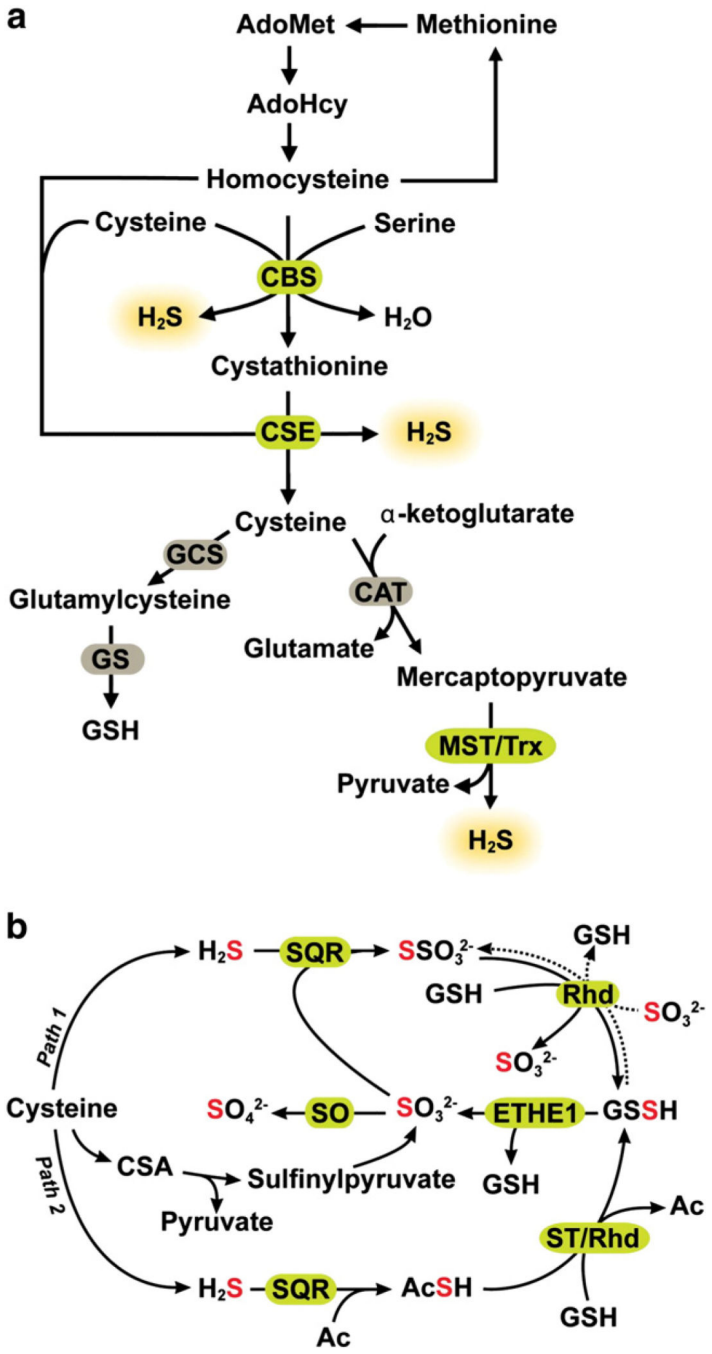

Fig. 2.

Pathways for sulfide biogenesis and clearance. (a) H_2S is synthesized from the amino acids, cysteine and homocysteine via the transsulfuration pathway enzymes, CBS and CSE and by the action of CAT, MST and thioredoxin (Trx) as described in the text. (b) Sulfide oxidation occurs in the mitochondrion. While the first reaction is catalyzed by SQR, the subsequent steps in the pathway remain to be defined. In “path 1” sulfite is shown as the acceptor of sulfane sulfur from SQR while in “path 2”, the acceptor (Ac) is not known and is an intermediate carrier of the sulfane sulfur between SQR and glutathione. The following new

abbreviations are used in the figure: Ac (acceptor), GCS (γ-glutamylcysteine synthetase), GS (glutathione synthetase), Rhd (rhodanese), ST (sulfurtransferase).

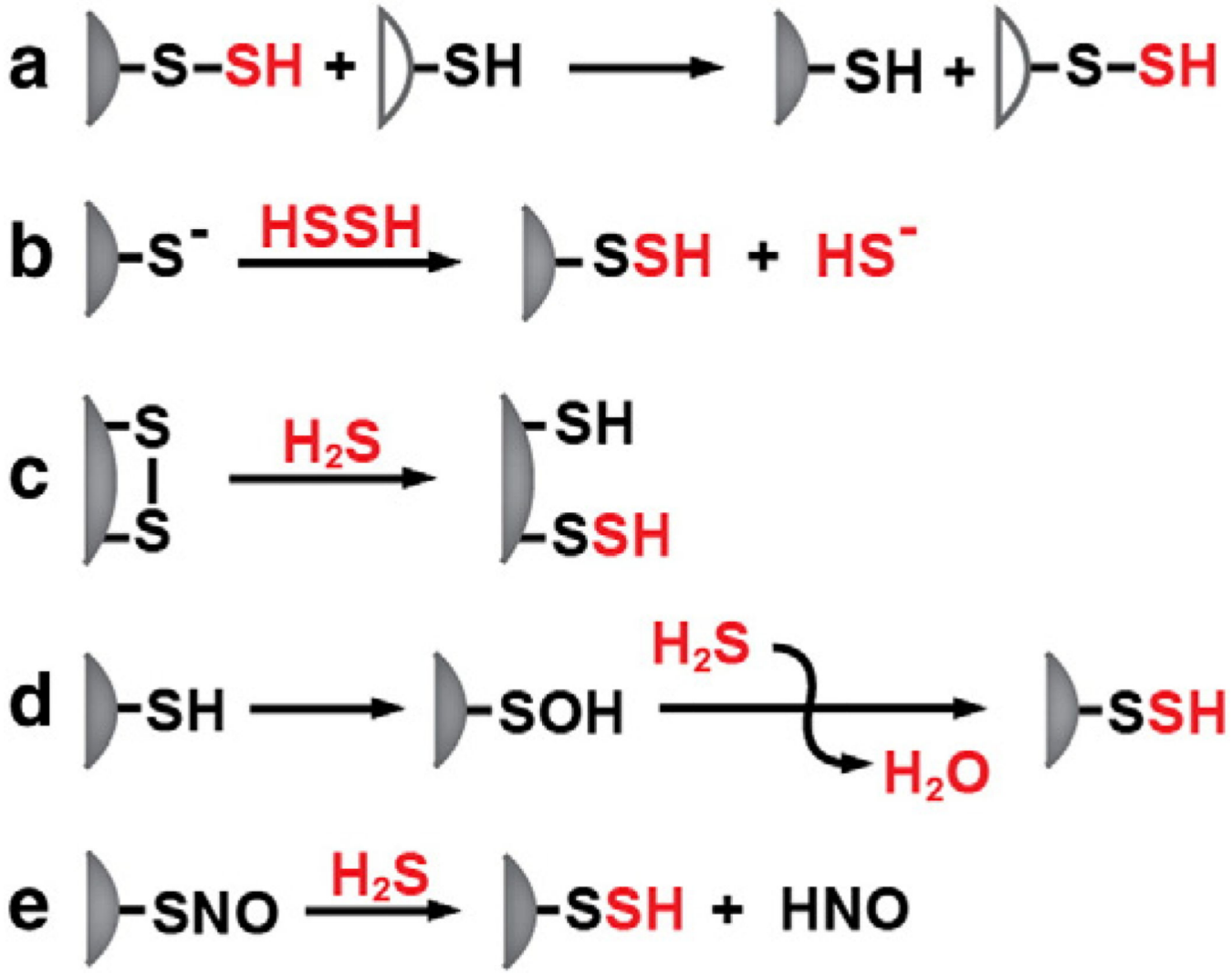

Fig. 3.

Alternative mechanisms for persulfidation. Persulfidation can occur by transsulfuration in which a small molecule or protein persulfide donor transfers the sulfane sulfur to an acceptor (a), by reaction of a protein thiolate with H_2S_2 (b), by attack of sulfide on a disulfide (c), by attack of sulfide on cysteine sulfenic acid or (d) by attack of sulfide on cysteine-S-nitrosothiol.

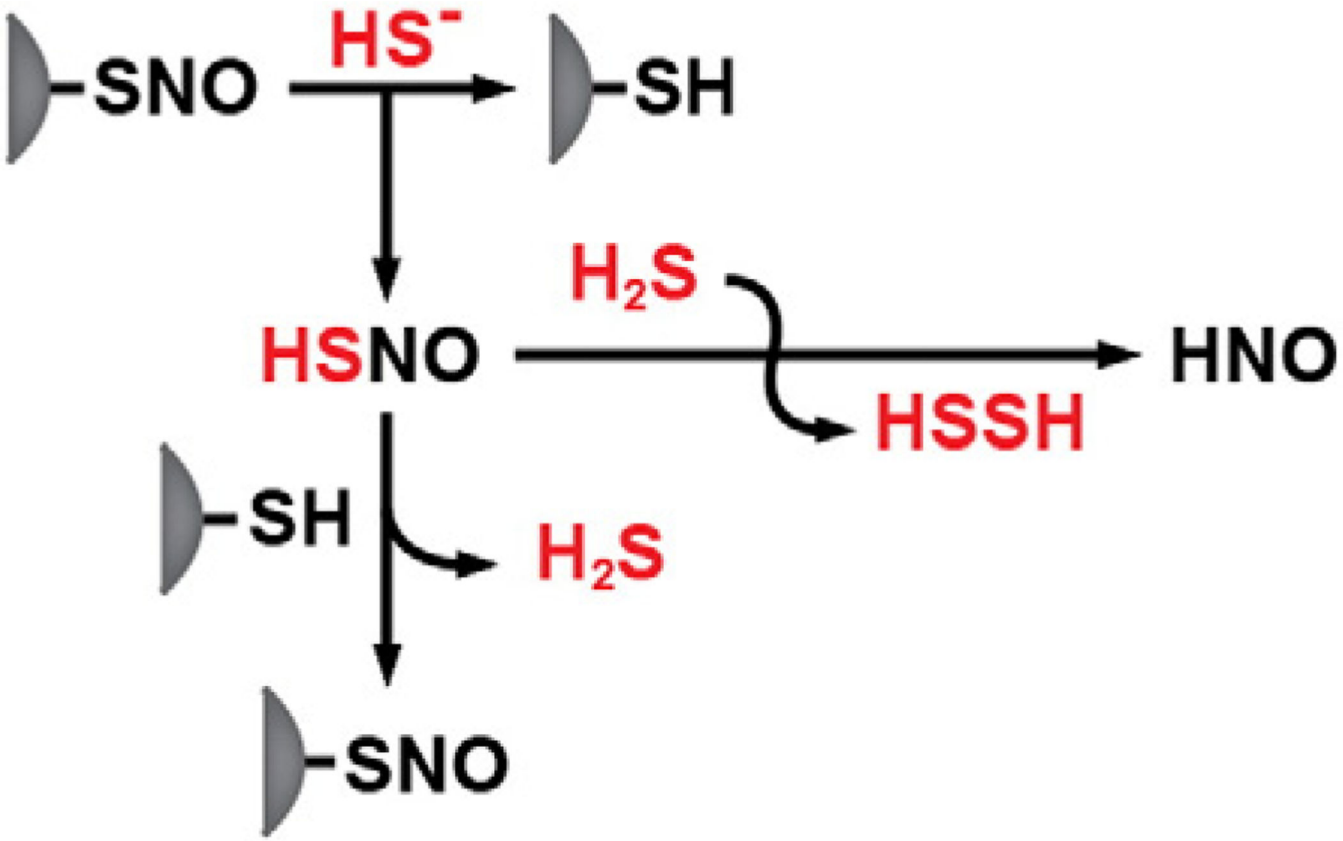

Fig. 4.

Mechanism for crosstalk between NO and H_2S signaling pathways. S-nitrosothiol (HSNO) canbeformed via transnitrosylation and can itself be a donor in anitrosylation reaction or can react with a second mole of H_2S generating HNO.

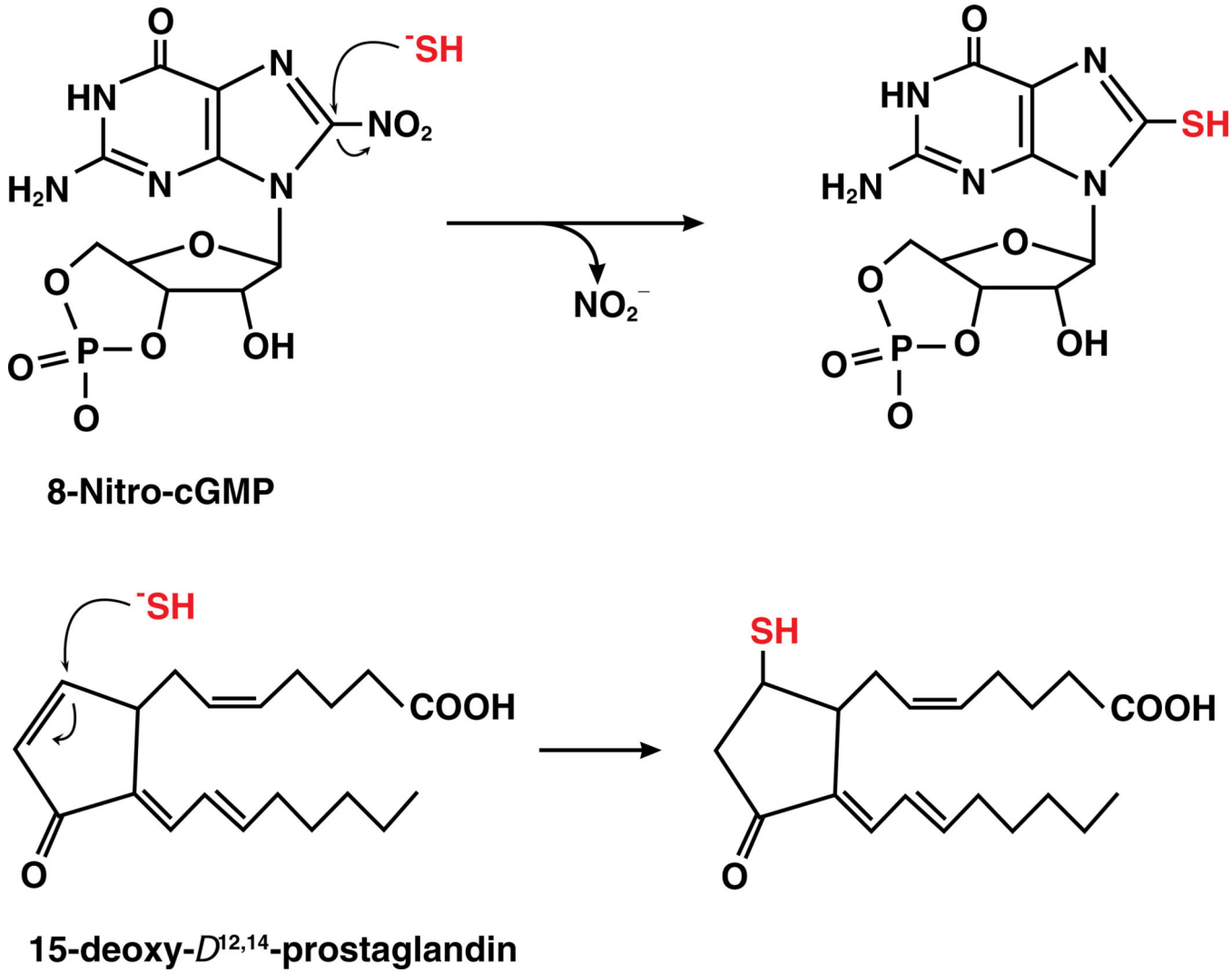

Fig. 5.

Reaction of H_2S with electrophiles. Sulfide can attack electrophiles like 8-nitro-cGMP to form 8-HS-cGMP (top) or fatty acids like 15-deoxy-$\Delta^{12,14}$-prostaglandin to form the thio-adduct.

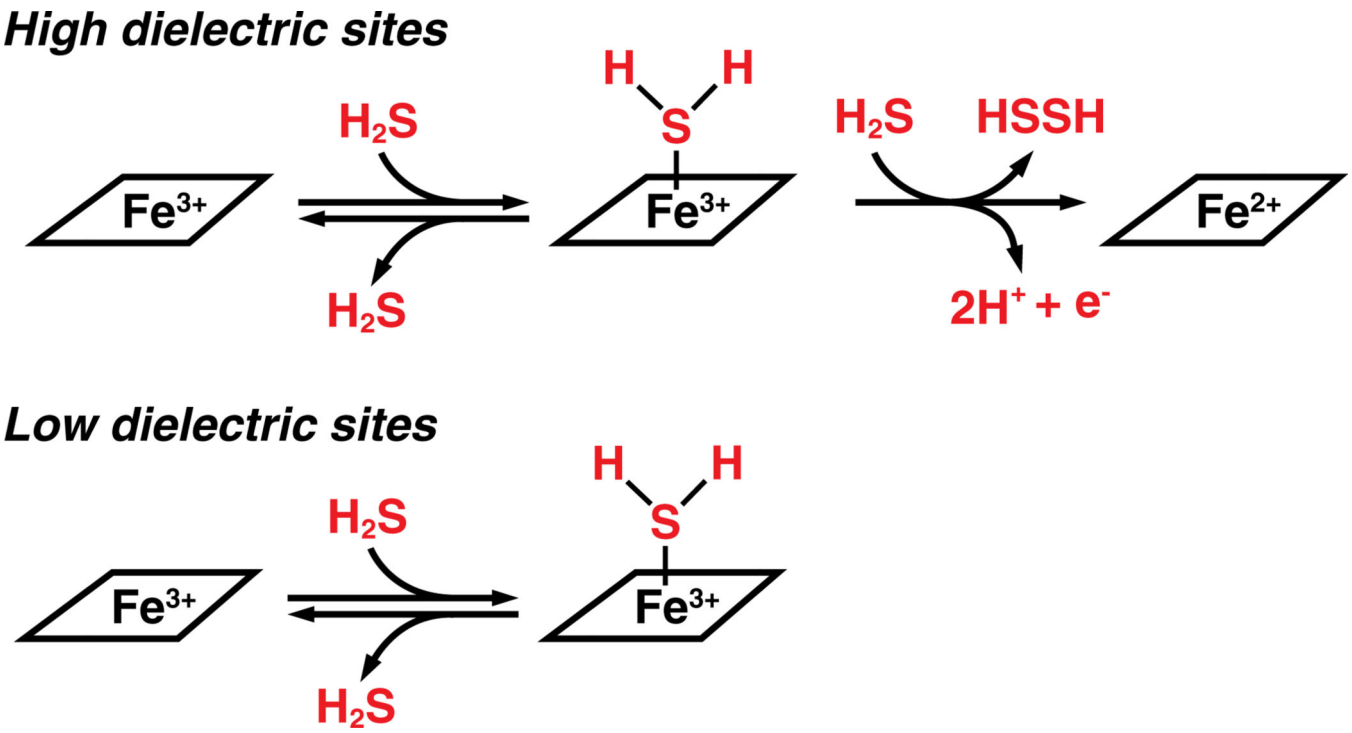

Fig. 6.

The reaction of H_2S with heme is dictated by the polarity of the heme pocket. A high dielectric (or polar) site favors reduction to ferrous heme whereas a low dielectric (or non-polar) site favors coordination to ferric heme.