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Review Article

Redox chemistry and chemical biology of H_2S, hydropersulfides, and derived species: Implications of their possible biological activity and utility

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ABSTRACT

Hydrogen sulfide (H_2S) is an endogenously generated and putative signaling/effector molecule. Despite its numerous reported functions, the chemistry by which it elicits its functions is not understood. Moreover, recent studies allude to the existence of other sulfur species besides H_2S that may play critical physiological roles. Herein, the basic chemical biology of H_2S as well as other related or derived species is discussed and reviewed. This review particularly focuses on the per- and polysulfides which are likely in equilibrium with free H_2S and which may be important biological effectors themselves.

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Abbreviations: sGC, soluble guanylate cyclase; NHE, normal hydrogen electrode; $MbFe^{III}$, methemoglobin; HbI, H_2S-binding hemoglobin; MPO, myeloperoxidase; $HbFe^{II}$–O_2, oxyhemoglobin; sulfHb, sulfhemoglobin; sulfMb, sulfmyoglobin; CcO, cytochrome *c* oxidase; SQR, sulfide:quinone oxidoreductase; CSE, cystathionine γ-lyase; CBS, cystathionine β-synthase; Trx1, thioredoxin; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; 8-NO_2-cGMP, 8-nitro-cyclic guanosine monophosphate; BDE, bond dissociation energy; NHE, normal hydrogen electrode

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Introduction

Hydrogen sulfide (H_2S) has been reported to be an important, endogenously generated, small-molecule signaling agent with numerous physiological functions (for recent reviews, see [1–4]). It is proposed to be one of the so-called "gasotransmitters"[1] along with nitric oxide (NO), carbon monoxide (CO), dioxygen (O_2), and derived species (for example, [5,6]). Although the reported functions of H_2S are numerous, the chemical mechanisms associated with its biological activity are not established. Moreover, the actual levels of H_2S present in biological tissues and fluids have been a matter of some contention and controversy [7,8] with early reports of levels as high as 20–80 μM in plasma. However, it is becoming increasingly clear that concentrations of "free" H_2S are low (submicromolar) but that there is a labile "pool" of sulfur-containing species, in equilibrium with free H_2S, that can liberate H_2S [9]. The fact that there is this large labile pool of H_2S-releasing species indicates likely biological significance to these H_2S precursor molecules (*vide infra*).

As with all biological signaling species, the utility of the small-molecule signaling agents is due to their unique chemistry and physical properties. That is, the signaling properties of these species are due to their specific/selective chemical interactions with biological targets and subsequent effects on the function of these target molecules (for example, [10]). The best and most established example of this (at least among the small-molecule signaling agents) is the interaction of NO with its primary biological target, the enzyme-soluble guanylate cyclase (sGC). The regulatory heme of sGC binds NO, which presumably results in the loss of an iron heme axial histidine ligand leading to activation of the enzyme. Significantly, NO appears unique in its ability to elicit this type of chemistry (dissociation of the axial ligand on ligand binding [11]). Unlike NO, the exact nature of the chemistry associated with the biological activity of H_2S is not firmly established. However, considering the fact that H_2S is first and foremost a simple thiol, it may be expected that the chemical biology of H_2S involves, at least in part, its properties as a nucleophile/reductant which can lead to changes in sulfur oxidation state. After all, much of the biological utility of thiols relies on these properties and interaction with other thiol species or metals. Thus, this review will focus on the biological chemistry of H_2S (and more importantly, species derived from H_2S or possibly those that can serve as sources of H_2S such as enzyme-mediated persulfide formation, *vide infra*) as a means to begin to understand its biological function and utility.

Although one of the focuses of this review is H_2S chemical biology, readers will note that the majority of the discussion presented herein relates to other sulfur species. This may seem curious considering the title of this review and the prevalence of the recent literature that mostly focuses primarily on H_2S. Therefore, before continuing further, it is worth presenting one of the tenets of this review: Some of the biological signaling/effects commonly associated with H_2S may be due to other sulfur-containing species which can degrade to release H_2S (making H_2S a possible marker for these species). In studies involving pharmacological or experimental addition of H_2S (or H_2S donors), the primary effector molecule may also not be H_2S, but rather these same species made via reaction of exogenous H_2S with oxidized thiol precursor species (*vide infra*). This is, of course, speculative at this time but justifies the time spent discussing other chemical species besides H_2S. This is not to say that H_2S is biologically innocuous. On the contrary, it seems likely that biological H_2S generation has function. What is being considered herein, however, is that other sulfur-containing molecules have unique and biologically important properties that allow them to be specific effector/signaling species. The fact that they may release H_2S under certain conditions may be biologically relevant since, considering the parsimony of Nature, it seems probable that H_2S release is also purposeful. Regardless, discussions of the chemistry of many of the sulfur species besides H_2S are given to provide the basis of future work/discussion of this signaling.

Nomenclature

As with many fields, unwieldy, inappropriate, or inconsistent terminology can be a major obstacle to understanding the chemistry being described. This seems especially true when describing the chemistry/biology of sulfur-containing molecules. For example, the terms thiol, sulfhydryl, and mercaptan have been used to denote essentially the same functional group, -SH. Although there are published rules or guidelines for the naming of sulfur-containing molecules (for example, [12]) they often do not cover all the possible sulfur-containing species and many of these rules are not rigorously followed or are cumbersome. To be sure, this review is not intended to serve as a treatise of sulfur nomenclature. However, it is worthwhile to define the terms that will be used herein to avoid confusion. Consistent with most of the current literature, the terms hydrogen sulfide, thiol, and disulfide will be used to describe H_2S, RSH, and RSSR, respectively. Hydrosulfide and sulfide are often used to specifically denote the anionic species HS^- (i.e., sodium hydrosulfide, NaHS) and S^{2-} (i.e., sodium sulfide, Na_2S). When the general term hydrogen sulfide is used, especially pertaining to its presence in biological systems, this will include all protonation states (H_2S, HS^-, and S^{2-}). Confusion can occur when referring to multisulfur species. The term alkyl hydropersulfide denotes a molecule whereby a disulfide is substituted on one end with an alkyl group and the other end with a hydrogen atom (RSSH). The term "alkyl hydrodisulfide" could have been used here (consistent with the naming of RSSR a disulfide) but since it is important to draw some structural and chemical analogy to peroxides (dialkyl peroxide, ROOR; alkyl hydroperoxide, ROOH; and hydrogen peroxide, HOOH) the term "persulfide" was selected (note that "perthiol" can also be used here, but for the sake of consistency this term will not be used; however, when referring to the radical RSS·, "perthiyl" is used). The term alkyl hydropolysulfides is used to describe species of the general form RSS_nH ($n > 1$). When referring to a specific polysulfide, the number of sulfur atoms can be indicated (e.g., RSSSH can be referred to as an alkyl hydrotrisulfide). A similar system for dialkyl polysulfides

[1] The term "gasotransmitter" is a poor description of these small-molecule signaling agents since it misrepresents their chemical state when they are acting biologically. They do *not* exist as gases, but as solutes when they are acting as physiological effector/signaling agents. This term is only noted here due to its unfortunate prevalence in the current literature.

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