
Preface

Hydrogen sulfide (H_2S) is a toxic gas that emits an unpleasant smell like rotten eggs. About 20 years ago, the mere presence of a pungent gas was considered as a physiological mediator. Following the discovery of endogenous sulfide in the mammalian brain, we found that H_2S is produced by the enzyme cystathionine β -synthase (CBS) and that it functions as a neuromodulator by enhancing the activity of neurotransmitter receptors in the brain. We found another H_2S -producing enzyme called cystathionine γ -lyase (CSE) in tissues, including vasculature. Another interesting observation was that H_2S could function as a smooth muscle relaxant. Although these enzymes were known to produce H_2S in vitro, H_2S was considered as a by-product of the metabolic pathways or as a marker for the evaluation of enzyme activity. Similar to CBS and CSE, 3-mercaptopyruvate sulfurtransferase (3MST) also produces H_2S , but its activity requires reducing cofactors such as thioredoxin and dihydrolipoic acid. Recently, we identified a fourth pathway of H_2S synthesis from D-cysteine. The enzymes described above are expressed in various tissues, including neurons, glia, vasculature, liver, kidney, pancreas, and the gastrointestinal tract. H_2S performs numerous activities in these organs, including neuromodulation, vascular relaxation, angiogenesis, energy formation in mitochondria, and protection against oxidative stress and ischemia–reperfusion injury. Owing to these beneficial effects of H_2S , H_2S -releasing drugs have been developed, and several of them are under clinical trials.

Ruma Banerjee and colleagues describe how endogenous levels of H_2S are enzymatically regulated for proper functioning, in their chapter “Enzymology of Hydrogen Sulfide Turnover.” Three pathways for H_2S production from L-cysteine as a major substrate are known, involving CBS, CSE, and 3MST along with cysteine aminotransferase (CAT), which is identical to aspartate aminotransferase (AAT). Since the H_2S elimination pathway is activated at considerably lower sulfide concentrations, the half-life of H_2S is short. This regulation enables H_2S to function as a signaling molecule. This chapter focuses on the structural enzymology and regulation of H_2S metabolism.

Ken Olson, in his chapter “Hydrogen Sulfide as an Oxygen Sensor,” describes that eukaryotic cells can detect O_2 availability and transduce it into physiological signals for the proper delivery of O_2 and regulation of O_2 consumption. Tissue H_2S concentrations are inversely related to O_2 concentrations. This reciprocal relationship between H_2S and O_2 indicates the similarity between the effect of hypoxia and

that of H_2S . Since H_2S is used by mitochondria to produce ATP along with O_2 consumption, mitochondria can be the site of O_2 sensing. Therefore, the O_2 -dependent metabolism of H_2S may be an effective O_2 -sensing mechanism. The determination of this mechanism at the subcellular level will be an additional evidence to strongly support this hypothesis.

In the chapter “Multiple Roles of H_2S in Inflammation: A New Class of Therapeutics,” Philip Moore and colleagues describe the ability of H_2S to promote the resolution of an inflammatory response and the potential of H_2S -targeting drugs for the treatment of inflammation. They show the importance of H_2S donor concentrations and the timing of their application in an ongoing inflammatory response, which consists of a sequence of processes: initiation, sustaining, and resolving inflammation. Each phase of the inflammatory response includes blood vessel dilatation, adhesion and migration of leukocytes, edema and pain, and the target of H_2S changes depending on the phase of inflammation. The interaction between endogenous and exogenous H_2S is also an intriguing problem that needs to be solved.

In the chapter “Signaling Mechanisms Underlying the Hydrogen Sulfide Effects: Identification of Hydrogen Sulfide ‘Receptor,’” Yi-Chun Zhu has summarized a mechanism for the structural modification of proteins to change their activity by H_2S by using a representative targeting molecule – vascular endothelial growth factor receptor (VEGFR), which induces angiogenesis by H_2S stimulation. H_2S breaks the cysteine disulfide bond in VEGFR, whereas S-sulphydrated cysteine, which is shortly observed, is immediately attacked by a second HS^- and reduced to cysteine. Breaking the cysteine disulfide bond is a reducing reaction, whereas S-sulphydration is an oxidizing reaction. Considering the fact that H_2S is a reducing molecule, the reduction of cysteine disulfide bond by H_2S is a plausible modification compared to S-sulphydration.

John Wallace and his colleague in their chapter “Therapeutic Applications of Hydrogen Sulfide” describe the development of drugs, which release appropriate amounts of H_2S at the proper target for a desirable period, on the basis of their functional mechanism rather than their observed effects. H_2S -based experimental drugs for arthritis, inflammatory bowel disease, oxidative stress-induced injury, and even cancer chemoprevention have been developed, and some of them are already entering clinical trials. Companies that have developed H_2S -based compounds aiming at the therapy of various disorders are also outlined in this chapter.

Jin-Song Bian and his colleague describe the biological function of H_2S in both health and disease, with special emphasis on its protective effects on tissues or organs in cardiovascular, central nervous, and renal systems in the chapter entitled “Hydrogen Sulfide: Physiological and Pathophysiological Functions.” Owing to the antioxidant, anti-inflammatory, and anti-apoptotic effects, manipulation of the H_2S system is implicated in the therapeutic benefits to patients suffering from various diseases. Research efforts have focused on the development of slow-releasing H_2S donors that mimic endogenous release of H_2S and the selective inhibitors of H_2S -producing enzymes.

Fumito Ichinose, in his chapter entitled “Biological Effects of H₂S Inhalation and Its Therapeutic Potential,” describes the beneficial effect of H₂S inhalation in various pathological conditions. The induction of a suspended animation-like metabolic state characterized by reduced energy consumption and hypothermia was observed in rodents, but not in larger animals. The beneficial effects against inflammation, ischemia–reperfusion injury, neurodegenerative diseases, and acute lung injury have a different mechanism from the induction of animation-like state because these effects are observed without any accompanied reduction in metabolism. However, a clear demonstration of these effects is required in larger animals to promise their therapeutic potential. The beneficial effects of inhaled H₂S are critically reviewed in this chapter.

Evgeny Nudler and his colleague in their chapter “H₂S as a Bacterial Defense Against Antibiotics” describe that H₂S produced by bacterial orthologs of the mammalian enzymes CBS, CSE, and 3MST has a role in the defense system against antibiotics. Homologs of nitric oxide synthase exist in a limited number of gram-positive species, whereas those of H₂S-producing enzymes are widely conserved in most bacterial species. Comprehensive understanding of H₂S mechanism provides a new target for drug development against infectious diseases.

In the final chapter, “Hydrogen Sulfide-Mediated Cellular Signaling and Cytoprotection,” Hideo Kimura describes H₂S-producing pathways, including a novel pathway with D-cysteine as the substrate. The D-cysteine pathway produces 80 times greater quantity of H₂S than that produced from L-cysteine in the kidney, and it effectively protects the organ from ischemia–reperfusion injury. It provides a new therapeutic approach to renal diseases. He also describes his recent finding that polysulfides, which are derived from H₂S, are found in the brain and activate transient receptor potential ankyrin 1 (TRPA1) channels in glia more potently than parental H₂S. Polysulfides may be responsible for some activities that have previously been ascribed to H₂S.

This book summarizes the recent progress in the study of H₂S, its functions in organisms ranging from bacteria to mammals, and its therapeutic applications. H₂S plays an important role in both physiological and pathophysiological conditions. Although the functional forms of H₂S, HS, and S²⁻ have not been determined, H₂S-derived polysulfides have been added as another active form of this molecule. By understanding the biochemical nature of these molecules, as well as their mechanisms of action, the physiological function and therapeutic potential of H₂S and related molecules will be unveiled.

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