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## Preface

Hydrogen sulfide ( $\text{H}_2\text{S}$ ) 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  $\text{H}_2\text{S}$  is produced by the enzyme cystathionine  $\beta$ -synthase (CBS) and that it functions as a neuromodulator by enhancing the activity of neurotransmitter receptors in the brain. We found another  $\text{H}_2\text{S}$ -producing enzyme called cystathionine  $\gamma$ -lyase (CSE) in tissues, including vasculature. Another interesting observation was that  $\text{H}_2\text{S}$  could function as a smooth muscle relaxant. Although these enzymes were known to produce  $\text{H}_2\text{S}$  in vitro,  $\text{H}_2\text{S}$  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  $\text{H}_2\text{S}$ , but its activity requires reducing cofactors such as thioredoxin and dihydrolipoic acid. Recently, we identified a fourth pathway of  $\text{H}_2\text{S}$  synthesis from D-cysteine. The enzymes described above are expressed in various tissues, including neurons, glia, vasculature, liver, kidney, pancreas, and the gastrointestinal tract.  $\text{H}_2\text{S}$  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  $\text{H}_2\text{S}$ ,  $\text{H}_2\text{S}$ -releasing drugs have been developed, and several of them are under clinical trials.

Ruma Banerjee and colleagues describe how endogenous levels of  $\text{H}_2\text{S}$  are enzymatically regulated for proper functioning, in their chapter “Enzymology of Hydrogen Sulfide Turnover.” Three pathways for  $\text{H}_2\text{S}$  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  $\text{H}_2\text{S}$  elimination pathway is activated at considerably lower sulfide concentrations, the half-life of  $\text{H}_2\text{S}$  is short. This regulation enables  $\text{H}_2\text{S}$  to function as a signaling molecule. This chapter focuses on the structural enzymology and regulation of  $\text{H}_2\text{S}$  metabolism.

Ken Olson, in his chapter “Hydrogen Sulfide as an Oxygen Sensor,” describes that eukaryotic cells can detect  $\text{O}_2$  availability and transduce it into physiological signals for the proper delivery of  $\text{O}_2$  and regulation of  $\text{O}_2$  consumption. Tissue  $\text{H}_2\text{S}$  concentrations are inversely related to  $\text{O}_2$  concentrations. This reciprocal relationship between  $\text{H}_2\text{S}$  and  $\text{O}_2$  indicates the similarity between the effect of hypoxia and

that of  $\text{H}_2\text{S}$ . Since  $\text{H}_2\text{S}$  is used by mitochondria to produce ATP along with  $\text{O}_2$  consumption, mitochondria can be the site of  $\text{O}_2$  sensing. Therefore, the  $\text{O}_2$ -dependent metabolism of  $\text{H}_2\text{S}$  may be an effective  $\text{O}_2$ -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  $\text{H}_2\text{S}$  in Inflammation: A New Class of Therapeutics,” Philip Moore and colleagues describe the ability of  $\text{H}_2\text{S}$  to promote the resolution of an inflammatory response and the potential of  $\text{H}_2\text{S}$ -targeting drugs for the treatment of inflammation. They show the importance of  $\text{H}_2\text{S}$  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  $\text{H}_2\text{S}$  changes depending on the phase of inflammation. The interaction between endogenous and exogenous  $\text{H}_2\text{S}$  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  $\text{H}_2\text{S}$  by using a representative targeting molecule – vascular endothelial growth factor receptor (VEGFR), which induces angiogenesis by  $\text{H}_2\text{S}$  stimulation.  $\text{H}_2\text{S}$  breaks the cysteine disulfide bond in VEGFR, whereas S-sulphydrated cysteine, which is shortly observed, is immediately attacked by a second  $\text{HS}^-$  and reduced to cysteine. Breaking the cysteine disulfide bond is a reducing reaction, whereas S-sulphydration is an oxidizing reaction. Considering the fact that  $\text{H}_2\text{S}$  is a reducing molecule, the reduction of cysteine disulfide bond by  $\text{H}_2\text{S}$  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  $\text{H}_2\text{S}$  at the proper target for a desirable period, on the basis of their functional mechanism rather than their observed effects.  $\text{H}_2\text{S}$ -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  $\text{H}_2\text{S}$ -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  $\text{H}_2\text{S}$  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  $\text{H}_2\text{S}$  system is implicated in the therapeutic benefits to patients suffering from various diseases. Research efforts have focused on the development of slow-releasing  $\text{H}_2\text{S}$  donors that mimic endogenous release of  $\text{H}_2\text{S}$  and the selective inhibitors of  $\text{H}_2\text{S}$ -producing enzymes.

Fumito Ichinose, in his chapter entitled “Biological Effects of H<sub>2</sub>S Inhalation and Its Therapeutic Potential,” describes the beneficial effect of H<sub>2</sub>S 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 H<sub>2</sub>S are critically reviewed in this chapter.

Evgeny Nudler and his colleague in their chapter “H<sub>2</sub>S as a Bacterial Defense Against Antibiotics” describe that H<sub>2</sub>S 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 H<sub>2</sub>S-producing enzymes are widely conserved in most bacterial species. Comprehensive understanding of H<sub>2</sub>S 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 H<sub>2</sub>S-producing pathways, including a novel pathway with D-cysteine as the substrate. The D-cysteine pathway produces 80 times greater quantity of H<sub>2</sub>S 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 H<sub>2</sub>S, are found in the brain and activate transient receptor potential ankyrin 1 (TRPA1) channels in glia more potently than parental H<sub>2</sub>S. Polysulfides may be responsible for some activities that have previously been ascribed to H<sub>2</sub>S.

This book summarizes the recent progress in the study of H<sub>2</sub>S, its functions in organisms ranging from bacteria to mammals, and its therapeutic applications. H<sub>2</sub>S plays an important role in both physiological and pathophysiological conditions. Although the functional forms of H<sub>2</sub>S, HS, and S<sup>2-</sup> have not been determined, H<sub>2</sub>S-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 H<sub>2</sub>S and related molecules will be unveiled.

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