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Review

Gasotransmitter hydrogen sulfide signaling in neuronal health and disease

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ABSTRACT

Hydrogen sulfide is a gaseous signaling molecule or gasotransmitter which plays important roles in a wide spectrum of physiologic processes in the brain and peripheral tissues. Unlike nitric oxide and carbon monoxide, the other major gasotransmitters, research on hydrogen sulfide is still in its infancy. One of the modes by which hydrogen sulfide signals is via a posttranslational modification termed sulfhydration/persulfidation, which occurs on reactive cysteine residues on target proteins, where the reactive —SH group is converted to an —SSH group. Sulfhydration is a substantially prevalent modification, which modulates the structure or function of proteins being modified. Thus, precise control of endogenous hydrogen sulfide production and metabolism is critical for maintenance of optimal cellular function, with excess generation and paucity, both contributing to pathology. Dysregulation of the reverse transsulfuration pathway which generates hydrogen sulfide occurs in several neurodegenerative diseases such as Parkinson's disease, Huntington's disease and Alzheimer's disease. Accordingly, treatment with donors of hydrogen sulfide or stimulation of the reverse transsulfuration have proved beneficial in several neurodegenerative states. In this review we focus on hydrogen sulfide mediated neuronal signaling processes that contribute to neuroprotection.

Contents

Abbreviations: 3-MST, 3-mercaptopyruvate sulfurtransferase; 4-HNE, 4-hydroxynonenal; 6-OHDA, 6-hydroxydopamine; Aβ, β-Amyloid; AD, Alzheimer's disease; ALS, Amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APP, Amyloid precursor protein; ATF4, Activating transcription factor 4; BACE1, β-secretase 1; CAT, Cysteine aminotransferase; CBS, Cystathionine β-synthase; CO, Carbon monoxide; CoQ, Coenzyme Q; CSE, Cystathionine γ-lyase; EAAT3, Excitatory amino acid transporter 3; EDRF, Endothelial derived relaxation factor; fALS, Familial Amyotrophic lateral sclerosis; GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; GH, Growth hormone; GluA1, Glutamate receptor subunit A1; H_2S, Hydrogen sulfide; HD, Huntington's disease; HFS, High frequency stimulation; Keap1, Kelch-like ECH associated protein 1; LTP, Long-term potentiation; MDA, Malondialdehyde; mTOR, mechanistic target of rapamycin; NaHS, Sodium hydrogen sulfide; NMDA, N-methyl-D-aspartate; NO, Nitric Oxide; NR2B, N-methyl D-aspartate receptor subtype 2B; Nrf2, Nuclear factor erythroid 2-related factor 2; PLP, Pyridoxal 5-phosphate; PD, Parkinson's disease; pKa, Acid dissociation constant; PLP, Prop-1, Prophet of Pit-1; PS1, Presenilin 1; PTEN, phosphatase and tensin homolog deleted on chromosome 10; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; SAM, S-adenosyl methionine; SP1, Specificity Protein 1; SQR, Sulfide:quinone oxidoreductase; SR, Serine racemase; SRB, Sulfate reducing bacteria, TRP14, Thioredoxin-related protein of 14 kDa; TrxR1, Thioredoxin reductase-1; TSH, Thyroid stimulating hormone; WRN, Werner protein.

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1. Introduction

Ever since the discovery of hydrogen sulfide (H_2S) three centuries, ago in 1713, the conceptions of its functions have evolved in diverse directions [1]. H_2S was considered to be an environmental toxin before it was discovered to be produced endogenously. Associated with the smell of rotten eggs and sewers, H_2S was variously labeled as "swamp gas, marsh gas, sewer gas and stink damp". In nature, H_2S and its derivatives occur in volcanic gases, hot springs, cold springs, natural gas and are also produced by bacteria and higher organisms. The history of the earth is intimately linked to H_2S, with the early atmosphere being a predominantly reducing one with oxygen existing as a trace element. H_2S was utilized by several bacteria as a source of energy. As the atmosphere became oxygen rich, various oxidation products of sulfur emerged which contribute to a rich array of signaling metabolites. H_2S is now recognized as the third major gaseous signaling molecule or gasotransmitter akin to nitric oxide (NO) and carbon monoxide (CO) [2].

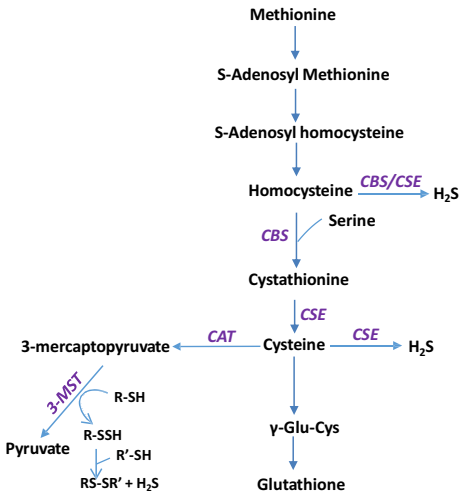

Fig. 1. Endogenous biosynthesis of hydrogen sulfide (H_2S) in mammals. H_2S is generated by three enzymes, cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST). Dietary methionine is converted to homocysteine, via the intermediates S-adenosylmethionine and S-adenosylhomocysteine, which is then condensed with serine by CBS to generate cystathionine, which is acted on by CSE to generate cysteine. Cysteine can either enter the glutathione biosynthetic pathway or be utilized as a substrate for H_2S biosynthesis. CBS generates H_2S efficiently from a combination of cysteine and homocysteine, whereas CSE can utilize either cysteine or homocysteine by itself to generate the gasotransmitter. The third enzyme 3-MST utilizes the 3-mercaptopyruvate generated by cysteine aminotransferase (CAT) by forming a persulfide on its active site (R-SH to R-SSH). The persulfide releases H_2S in the presence of a reductant (R′-SH).

H_2S is synthesized by three enzymes in mammals: cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (3-MST) which synthesize the gas using pyridoxal 5-phosphate (PLP) as a cofactor and cysteine as a substrate (Fig. 1). CSE acts on cysteine to produce H_2S, pyruvate and ammonia [3–7] and is present mostly in the peripheral tissues. CBS condenses cysteine and homocysteine to produce H_2S in addition to cystathionine. 3-MST generates H_2S in conjunction with cysteine aminotransferase (CAT). CAT metabolizes cysteine and α-ketoglutarate to form 3-mercaptopyruvate (3-MP). 3-MST utilizes the 3-MP formed to generate H_2S with pyruvate as a by-product. 3-MST also generates H_2S using D-cysteine as a substrate in conjunction with D-amino acid oxidase. CBS and 3-MST occur mostly in the central nervous system [8], although these enzymes are also present in peripheral tissues. In addition to these pathways, H_2S can be generated from the acid labile pool, consisting of iron-sulfur protein clusters and the sulfane sulfur pool, which functions in the presence of endogenous reductants [9]. The other important yet underappreciated source of H_2S is the microbiota that colonize the gut of mammals. Half of fecal H_2S is derived from commensal bacteria [10]. Sulfate-reducing bacteria (SRB), which include the genus *Desulfovibrio* predominantly produce H_2S in mammals [11,12]. H_2S produced by these bacteria may influence colon health and function. A sulfate-rich diet causes increased growth of *Desulfovibrio piger* and high rates of H_2S production in the colon of humans and mice. In addition, several anaerobic bacterial such as *Escherichia coli*, *Salmonella enterica*, *Clostridia* and *Enterobacter aerogenes* generate H_2S from cysteine by the enzymatic activity of cysteine desulfhydrase [13,14]. In addition to these pathways, H_2S may be generated by the action of sulfite reductase of the bacteria, *E. coli*, *Rhodococcus Salmonella*, *Enterobacter*, *Klebsiella*, *Bacillus*, *Staphylococcus* and *Corynebacterium* [15].

Study of H_2S in the central nervous system was triggered by the discovery of sulfides in the brain. In 1989, while studying H_2S poisoning, Warenycia and associates discovered that inhalation of H_2S resulted in an elevation of brain sulfide that was directly proportional to the dose of the gas inhaled and mortality in rats. More interestingly, untreated brain also revealed the presence of sulfide [16]. In two cases of fatal H_2S inhalation in humans, elevated levels of sulfide were detected [17], prompting detailed studies on H_2S biosynthesis in the brain. Expression of CBS was found to be high in the hippocampus and cerebellum and the production of H_2S was found to be dependent on the presence of cysteine and PLP. While the production of H_2S was significantly inhibited by the use of the CBS inhibitors, hydroxylamine and amino-oxyacetate, S-adenosyl methionine (SAM/AdoMet) stimulated CBS activity. Early studies reported higher concentrations of H_2S (50–160 μM) in the brains of mammals. These estimations employed, the methylene blue method, which uses harsh acidic conditions, thus including the H_2S released from acid labile sulfur and iron-sulfur clusters [18] leading to overestimates. Endogenous concentrations measured by other methods revealed much lower 10 nM to 3 μM levels [18,19].