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Review

Hydrogen sulfide: Neurochemistry and neurobiology

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Abstract

Current evidence suggests that hydrogen sulfide (H_2S) plays an important role in brain functions, probably acting as a neuromodulator as well as an intracellular messenger. In the mammalian CNS, H_2S is formed from the amino acid cysteine by the action of cystathionine β-synthase (CBS) with serine (Ser) as the by-product. As CBS is a calcium and calmodulin dependent enzyme, the biosynthesis of H_2S should be acutely controlled by the intracellular concentration of calcium. In addition, it is also regulated by *S*-adenosylmethionine which acts as an allosteric activator of CBS. H_2S, as a sulfhydryl compound, has similar reducing properties as glutathione. In neurons, H_2S stimulates the production of cAMP probably by direct activation of adenylyl cyclase and thus activate cAMP-dependent processes. In astrocytes, H_2S increases intracellular calcium to an extent capable of inducing and propagating a ''calcium wave'', which is a form of calcium signaling among these cells. Possible physiological functions of H_2S include potentiating long-term potentials through activation of the NMDA receptors, regulating the redox status, maintaining the excitatory/inhibitory balance in neurotransmission, and inhibiting oxidative damage through scavenging free radicals and reactive species. H_2S is also involved in CNS pathologies such as stroke and Alzheimer's disease. In stroke, H_2S appears to act as a mediator of ischemic injuries and thus inhibition of its production has been suggested to be a potential treatment approach in stroke therapy.

Keywords: Hydrogen sulfide; Cystathionine β-synthase; Neuromodulator; CNS; Stroke

Contents

Abbreviations: AOAA, aminooxyacetate; ATP, adenosine triphosphate; camp, cyclic adenosine monophosphate; $[Ca^{2+}]_i$, intracellular calcium concentration; CBS, cystathionine-β-synthase; β-CNA, β-cyano-L-alanine; CSE, cystathionine-γ-lyase; Cys, L-cysteine; GABA, γ-aminobutyric acid; $GABA_BR$, γ-aminobutyric acid B receptor subtype; Glu, L-glutamate; γ-GCS, γ-glutamylcysteine synthetase; GSH, glutathione; H_2O_2, hydrogen peroxide; H_2S, hydrogen sulfide; HA, hydroxylamine; Hcy, homocysteine; tHcy, plasma total homocysteine; HS^-, hydrosulfide anion; hyperHcy, hyperhomocysteinemia; LPS, lipopolysaccharide; LTP, long-term potentiation; MCAO, middle cerebral artery occlusion; Met, L-methionine; MTHFR, methylenetetrahydrofolate reductase; NaHS, sodium hydrosulfide; NH_3, ammonia; NMDA, *N*-methyl D-aspartate; NOS, nitric oxide synthase; PLP, pyridoxal-5′-phosphate; PAG, D,L-propargylglycine; PKA, protein kinase A; SAM, *S*-adenosylmethionine; Ser, L-serine; SOX, sulfite oxidase

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1. Introduction

Hydrogen sulfide (H_2S) is a poisonous gas used as a chemical reagent. It is a broad-spectrum toxicant as it affects most organ systems in the body. The early symptoms of H_2S exposure include sore throat, dizziness, nausea, and respiratory effects attributed to airway irritation. Acute exposure to H_2S exhibits a very steep dose–response relationship with an LD_{50} of 15 mg/kg (rats), especially for CNS and respiratory depression, which is the major cause of death in acute H_2S poisoning (Warenycia et al., 1989). The primary cause of death in H_2S poisoning has been attributed to respiratory paralysis (Beauchamp et al., 1984). In addition, pulmonary edema has consistently been reported as the single most notable lesion in autopsies of individuals killed by H_2S poisoning (Burnett et al., 1977). At present, although the mechanism of action for these toxic effects is not clear, it is widely believed that H_2S targets mitochondria at low micromolar concentrations via reversible inhibition of cytochrome *c* oxidase (Reiffenstein et al., 1992).

It had long been assumed that H_2S exists in animal tissues at very low concentrations because of its toxicity, although it could be produced endogenously. However, more recent studies have shown that H_2S is present in mammalian tissues at levels far higher than first expected, up to 50–160 μmol/L (Goodwin et al., 1989; Warenycia et al., 1989) as measured in rat, human and bovine brain tissues. Abe and Kimura (1996) have shown that sodium hydrosulfide (NaHS, an H_2S donor) at concentrations (10–130 μM) similar to the physiological concentrations of H_2S selectively enhances *N*-methyl D-aspartate (NMDA) receptor-mediated responses and facilitates the induction of hippocampal long-term potentiation (LTP). This review presents an overview of the current evidence that H_2S plays an important role in brain functions, probably acting as a neuromodulator and/or as an intracellular messenger (Moore et al., 2003).

2. Physical properties of H_2S

H_2S is the sulfur analog of water with a molecular weight of 34.08. But unlike water, it has weak intermolecular forces and thus exists in the gaseous form at room temperature and pressure. H_2S is a colorless gas characterized by its offensive odor described as the smell of rotten eggs. It can be oxidized by a variety of agents to form sulfur dioxide and sulfuric acid. In the mammalian body, at a physiological pH of 7.4, approximately one-third of H_2S exists as the un-dissociated form and two-thirds as the hydrosulfide anion (HS^-) (Reiffenstein et al., 1992). It can easily penetrate the plasma membranes of cells in the undissociated form because of its lipid solubility.

3. Biochemical pathways related to the production of H_2S

In mammalian tissues, two pyridoxal-5′-phosphate (PLP)-dependent enzymes – cystathionine-β-synthase (CBS, EC 4.2.1.22) and cystathionine-γ-lyase (γ-cystathionase CSE, EC 4.4.1.1) – are responsible for most of the biosynthesis of H_2S from L-cysteine (Cys). As shown in Fig. 1, H_2S is released from the desulfuration of Cys (Stipanuk and Beck, 1982). Firstly, Cys may be hydrolyzed by CBS to produce H_2S with L-serine (Ser) as the by-product or hydrolyzed by CSE to produce H_2S, pyruvate and ammonia (NH_3). Secondly, cystine (which is essentially two Cys molecules linked by a disulfide bridge) may be converted to form thiocysteine, pyruvate and NH_3 by CSE. Thiocysteine is then acted on by CSE to form Cys and H_2S, or with another thiol compounds (RSH, e.g. glutathione (GSH) or Cys) as a second substrate to form H_2S and CysSR. It is possible that the conversion of thiocysteine to Cys and H_2S may also occur non-enzymatically (Cavallini et al., 1962). These two key enzymes are also involved in the transsulfuration pathway of homocysteine (Hcy) metabolism with CBS catalyzing the condensation of Hcy and Ser to form cystathionine in an irreversible reaction. Cystathionine is then hydrolyzed by CSE to form Cys with α-ketobutyrate and NH_3 as by products (Fig. 1).

Besides the above, there are several additional pathways that have been described. Firstly, Cys may react with a ketoacid

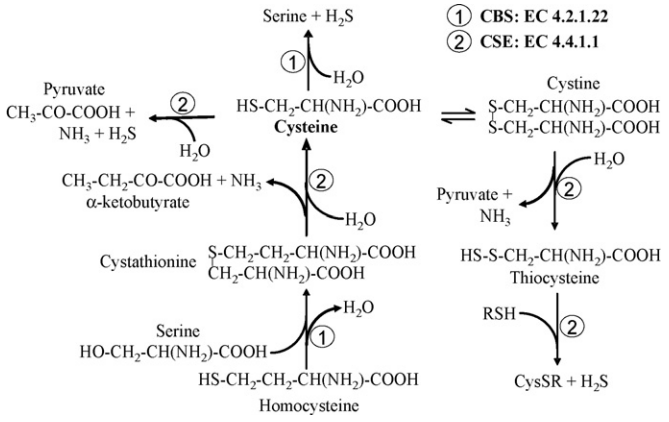

Fig. 1. Endogenous biosynthetic pathways of H_2S involving cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). RSH represents any thiol compound.