

H₂S: An Endogenous Gas

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ABSTRACT

Gases, such as NO and CO, play important roles both in normal physiology and in diseases. In recent years, interest has been directed towards other naturally-occurring gases, notably H₂S, which is produced in body by three enzymes, namely cystathionine beta synthase (CBS), cystathionine gamma lyase (CSE) and 3-Mercaptopyruvate sulfurtransferase (MST), present in mitochondria and/or cytosols where main substrate is L-cysteine. Recent studies have shown that vascular tissues generate measurable amount of H₂S. NO is considered as inducer for H₂S. H₂S has gained importance as a neuromodulator and a vasorelaxant factor and as the first endogenous gaseous ATP dependant K⁺ channel opener. It potentiates LTP by enhancing NMDA induced inward current. H₂S induces vasorelaxation, inhibits insulin secretion and also has a role in inflammation. H₂S also appear to have a role in neuroendocrine fuction because it plays an important role in control of the hypothalamus-pitutary-adrenal axis, inhibit stimulated release of corticotropin-releasing hormone. H₂S has been found to be decreased in patient with Alzheimer's disease and higher concentrations are found in patients with Down's syndrome. It has a role in development of hypertension, suggesting its role in CNS and CVS disorders. H₂S it is well known toxic gas with the smell of rotten eggs, is now proposed as a physiologically important molecule.

Keywords: *Hydrogen sulfide, ATP dependant K⁺ channel opener, Vasorelaxation*

Significant amount of H₂S is produced in various tissues. Recent studies have shown that vascular tissues generate measurable amount of H₂S. High concentration of H₂S has been observed in brain of rats, humans and cows. The H₂S concentration in rat serum is about 46 μM [1] and in brain tissue is about 50-160 mM [2]. In this review, the formation of H₂S along with its effect on body has been discussed, which has been depicted in Figure 1.

FORMATION OF H₂S

Several enzymes present in mammalian tissues catalyze the desulfhydration of cysteine. 3-Mercaptopyruvate sulfurtransferase (MST) is produced both in mitochondria and in the cytosol, where as cystathionine gamma lyase (CSE) and cystathionine beta synthase (CBS) are produced only in cytosol. The amount of the enzyme produced in mitochondria and cytosol varies depending on the species and organ.

CSE, a pyridoxal 5-phosphate-dependant enzyme, catalyzes the desulfhydration of cysteine which can be inhibited by D L-propargylglycine. A larger proportion of hydrogen sulfide production takes place in the liver. It catalyzes a β-disulfide elimination reaction that results in the production of pyruvate, NH₄⁺ and

thiocysteine. Thiocysteine may react with cysteine or other thiols to form hydrogen sulfide [3]. The enzyme activity is about 10 times higher in the rat liver than in the liver of full-term human infants and over 4 times higher than that in the adult human liver [4]. CSE activity in guinea pig is 5-fold lower in the liver and 18-fold lower in the kidney than those in rats [5]. CSE inhibitors do not suppress the production of H₂S in brain, but suppress its production in the liver and kidney. H₂S production in brain seems to be unrelated to CSE.

CBS, a pyridoxal 5-phosphate-dependent enzyme, can synthesize hydrogen sulfide from L-cysteine [3]. CBS is the main enzyme responsible for production of H₂S in the brain. H₂S is formed by the substitution of the thiol group of L-cysteine with a variety of thiol compounds to form the corresponding thioether. CBS is continuously produced at an especially-high level in the neural and cardiac systems [6]. CBS activity has been measured in various regions of developing rat brain; the activity gradually increases during development at almost the same rate in each region, until the adult level is reached at 4 weeks [7]. H₂S production from L-cysteine by brain homogenate is inhibited in the presence of CBS inhibitors, such as hydroxylamine and aminooxyacetate [8]. The activity of CBS is regulated presumably at tran-

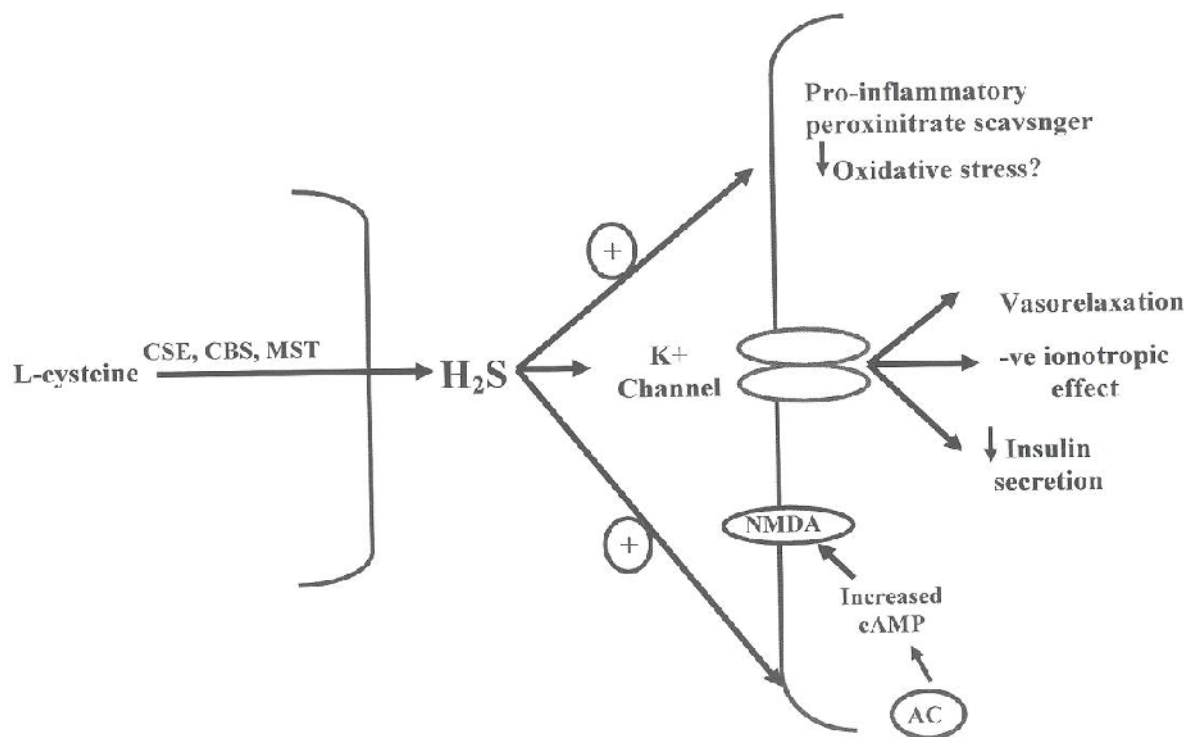


Fig 1. H₂S formation and its effect on various conditions in body. CSE:cystathionine gamma lyase, CBS: cystathionine beta synthase, MST:Mercaptopyruvate sulfurtransferase, NMDA: N-methyl-D-aspartate, AC: adenylyl cyclase, cAMP:, cyclic adenosine mono phosphate

scriptional level by glucocorticosteroids and cAMP. S-adenosyl L-methionine (SAM) enhances the affinity of the enzyme CBS by allosteric activation. SAM binds to the regulatory domain of CBS, then a conformational change occurs that frees the catalytic domain and CBS become active. In addition SAM and pyridoxal 5-phosphate, it was recently found that Ca²⁺/calmodulin-mediated pathways are involved in the regulation of CBS activity. In the absence of Ca²⁺/calmodulin, the c-terminal domain may cover the catalytic domain and CBS activity remains at a basal level. When Ca²⁺/calmodulin binds to a specific 19 amino-acid sequence, the catalytic domain is exposed by opening of c-terminal domain. CBS mutant, which is deficient in the 19 amino-acid Ca²⁺/calmodulin binding sequence, is constantly active, even in absence of Ca²⁺/calmodulin [9].

MST activity can be detected in mitochondria and cytosolic fractions of rat liver and kidney. MST, a zinc-dependent enzyme, is predominantly localized in proximal tubular epithelium in the kidney, pericentral hepatocytes in the liver, cardiac cells in the heart and neuroglial cells in the brain [10]. MST activity has been measured in various rat and guinea pig tissues. MST activity is sixty times lower in the guinea pig liver than in the rat liver. In mitochondria, MST can produce H₂S from 3-mercaptopyruvate. It also transfers its sulfur to sulfide from 3-mercaptopyruvate or transfers its sulfur to sulfite, which then forms thiosulfate. In the cytosol, the thiocysteine formed by CSE can act as an acceptor of the sulfur transferred from 3-mercaptopyruvate by

MST [11]. The higher sulfide production capacity of the liver and kidney is markedly inhibited by propargylglycine, a specific inhibitor of CSE, whereas L-aspartate, an inhibitor of the MST pathway, significantly inhibits sulfide production from L-cysteine in the heart but not in the liver or kidney. Thus, sulfide production is mainly due to CSE rather than MST activity in the whole body [11].

Also, H₂S is produced by non-enzymatically reduction of elemental sulfur to H₂S using reducing equivalents obtained from the oxidation of glucose. All essential components of this non-enzymatic pathway are present in vivo, including supply of reducible sulfur [12].

H₂S CATABOLISM

In vivo, H₂S is metabolized by oxidation in mitochondria or by methylation in cytosol. H₂S can be scavenged by methemoglobin or metallo- or disulfide-containing molecules such as oxidized glutathione. H₂S is excreted mainly by the kidney as free or conjugated sulfate. Thiosulfate is an intermediate in sulfide oxidation to sulfate. Two enzymes can act on thiosulfate, namely thiosulfate sulfurtransferase and thiosulfate reductase. One molecule of thiosulfate is formed from two molecules of H₂S [12].

EFFECTS OF H₂S

CARDIOVASCULAR SYSTEM

The presence of H₂S-producing enzyme and endogenous level of H₂S in cardiovascular system shows that

it has a role in the functioning of cardiovascular system. CSE expression and activity are found in rat portal vein and thoracic aorta. Expression levels of CSE mRNA varies in different types of vascular tissues, with intensity rank of pulmonary artery > aorta > tail artery > mesenteric artery [12]. The CBS does not have major role in H₂S production in cardiovascular system.

In both in vivo and in vitro experiments, H₂S has negative inotropic effect on heart. H₂S is considered as endogenous vasorelaxant factor and has a role in the maintaining blood pressure. I.V. bolus injection of H₂S decreases central venous pressure and production of endogenous H₂S. It is essential factor in the development of spontaneous hypertension [13]. Down-regulation of H₂S/CSE system is considered as a major factor in the development of spontaneous hypertension and the accompanying structural remodeling of aorta [14]. Exogenous administration of H₂S may attenuate the process of hypertension. Thus, exogenous H₂S provides a new way for interfering with the progression of hypertension. The hypotensive effect of H₂S was mimicked by pinacidil and antagonized by glibenclamide [15]. It has been shown by Weimin and Wang (2001) that vasorelaxant effect of H₂S is mainly mediated by an interaction of the gas with smooth muscle and partially by functional endothelium [16]. H₂S-induced relaxation of rat aortic tissues was mainly due to direct interaction of H₂S and SMCs, based on the failure of denervation of vascular tissues in vitro to alter H₂S effect and on the observation that H₂S still significantly relaxed vascular tissues after endothelium removal. A small portion of the H₂S-induced vasorelaxation was attenuated by removal of the endothelium or the application of L-NAME, an inhibitor of NO synthase, in the presence of the endothelium. This endothelium-dependent effect of H₂S could be explained by the release of endothelium derived vasorelaxant factors in response to H₂S stimulation because co-application of apamin and charybdotoxin, which can block the effect of endothelium-derived hyperpolarizing factor (EDHF), to the endothelium-intact rat aortic tissues reduced the vasorelaxant effect of H₂S. It seems that H₂S might release EDHF from vascular endothelium. The presence of an intact endothelium might serve as a buffer to retain H₂S in the blood vessel wall, so that its vasorelaxant effect can be potentiated and prolonged.

Unlike NO and CO, H₂S relaxed vascular tissues independent of the activation of cGMP pathway, where as vasorelaxation induced by NO was virtually abolished by sGC inhibitor ODQ, but ODQ potentiated vasorelaxant effect of H₂S. Hypothetically, the interaction between H₂S and ODQ may have generated vasorelaxant free radicals, which further relaxed vascular tissue [16].

The H₂S-induced vasorelaxation is dependant on extracellular entry of Ca²⁺ ions. By directly-acting on vascular SMCs, H₂S may reduce the extracellular calcium entry and relax vascular tissues. Both endothelium and vascular smooth muscles may serve as targets for H₂S. By acting on endothelium, H₂S may facilitate the release of vasorelaxant factors, including NO and EDHF

[16]. The most significant vascular effect of H₂S is dependent on K⁺/ATP channels. In vascular SMCs, H₂S-induced relaxation of the aortic tissues precontracted with phenylephrine was mimicked by K⁺/ATP channel opener, pinacidil, but it was concentration-dependently inhibited by glibenclamide. So, H₂S is the firstly-identified gaseous K⁺/ATP opener in vascular SMCs [15]. It has direct interaction with K⁺/ATP protein without affecting ATP concentration. The opening of K⁺/ATP channels leads to membrane hyperpolarization, which in turn may close voltage-gated calcium channel, thus reduce extracellular calcium entry. Alternatively, H₂S may directly inhibit voltage-gated Ca²⁺ channels in vascular SMCs [16], a possibility that requires further investigation. Hypotension is associated with haemorrhagic shock partly due to the release of endogenous H₂S. Since, H₂S is a vasodilator, it seems likely that overproduction of H₂S during haemorrhagic shock contributes to the hypotension observed [17]. Thus, inhibition of H₂S biosynthesis represents a novel approach to the treatment of haemorrhagic shock, because inhibition of cardiac H₂S biosynthesis might also be expected to improve cardiac output due to negative inotropic effect of H₂S. It is seen that endogenous vascular H₂S level is increased in rats with septic shock and endotoxic shock. So, it was suggested that endogenous H₂S was involved in pathophysiological process during shock [18]. Deficiency of H₂S may also contribute in pathophysiology of some diseases like atherosclerosis, in some patient with hyperhomocysteinemia, and in whom metabolism of homocysteine to cysteine and H₂S is compromised by vitamin B₆ deficiency [19].

CENTRAL NERVOUS SYSTEM

First evidence for physiological role of H₂S was obtained as early as in 1989. CBS and CSE gradually increased after birth and reached adult level at 2-4 week. In rat brain, activities of CBS and CSE in six different region were detected. The activity of CBS was 30 fold greater than CSE and based on Northern blot analysis, CBS is the major enzyme for H₂S production in brain [8]. Endogenous sulfide level in rat brain tissue (1.6 µg/g) and in normal human postmortem brain stem (0.7 µg/g) was also reported [12].

NaHS at physiologically relevant concentration induced a concentration-dependant (27-200 µM) hyperpolarization and reduced input resistance of CA1 neurons or dorsal raphe neurons. Changes in K⁺ conductance were identified to be the main ionic basis for these effects. Change in K⁺ conductance is due to the effect of K⁺/ATP channel, while the effect on calcium-activated K⁺ channel and voltage-dependant K⁺ channels were not supported. Voltage-dependent and TTX-sensitive Na⁺ channels may be targeted by H₂S in neurons. In cultured neuroblastoma cells, NaHS or taurine alone did not alter Na⁺ channel currents. After pretreatment of these cells with NaHS, taurine dramatically inhibited Na⁺ channels in a reversible fashion. This effect of NaHS was mimicked by disulfide reducing agents dithiothreitol and βmercaptoethanol. A reduction of disulfide bonds between Na⁺ channel subunits by H₂S was suggested as a

probable mechanism. It was also suggested that certain neuronal effects of H₂S could be mediated by the alteration in taurine levels, because taurine is an inhibitory neurotransmitter and a short exposure to NaHS resulted in a twofold increase of taurine in brainstem, but concentration used in the study was higher than physiological concentration [12].

H₂S also appears to have a role in neuroendocrine function because it plays an important role in the control of the hypothalamus-pituitary-adrenal axis. Indeed, increases in H₂S level in hypothalamus either obtained with H₂S-enriched media or by addition of the H₂S precursor S-adenosyl L-methionine are associated with inhibition of stimulated release of corticotrophin-releasing hormone from hypothalamic explants. In vivo experiments in rat under rest and after stress-induced adrenocorticle releasing activation show that S-adenosyl L-methionine significantly reduces the rise in serum corticosterone level which [20]. These results show pathophysiological importance of H₂S in regulation of neuroendocrine function. NMDA receptors are also target for H₂S, because LTP is altered in CBS knockout mice [21]. In the presence of weak titanic stimulation, NaHS facilitates LTP by enhancing NMDA-induced inward current and increased cAMP production [8,22]. It increased cAMP production in primarily cultured rat cerebral and cerebellar neurons or in selected rat brain neuronal and glial cell lines. All these observations confirm that H₂S have a role in some aspect of synaptic activity. Also, it was found that H₂S level decreased in patient with Alzheimer's disease. On the other hand, excess of H₂S may lead to mental retardation in patient with Down's syndrome [21], suggesting role of H₂S in CNS disease as a neuromodulator in the brain.

OTHER EFFECTS

H₂S also have other physiological and pathophysiological role in inflammation, diabetes and oxidative stress. Bhatia and co-workers showed the effect of H₂S in inflammatory conditions such as acute pancreatitis. According to their observation, prophylactic and therapeutic use of CSE inhibitor, DL-propargylglycine, significantly reduced the severity of caerulein-induced pancreatitis and associated lung injury. These effects of CSE blockade suggest an important proinflammatory role of H₂S in regulating the severity of pancreatitis and associated lung injury. This raises the possibility that H₂S may exert similar activity in other forms of inflammation [23].

H₂S, as a K⁺/ATP channel opener, may have effect on pancreatic K⁺/ATP channel. H₂S inhibits insulin secretion from pancreatic cell lines and it is high in insulin resistance condition [24]. According to our experiments, H₂S inhibits insulin secretion and its in vivo effect was inhibited by glibenclamide; which proves the effect of H₂S on pancreatic K⁺/ATP channel. Streptozotocin-induced diabetes in rats increase expression of CBS and CSE in liver, so H₂S level is also high in that diabetic rats, suggesting role of H₂S in pathophysiology of diabetes [25,26]. H₂S significantly inhibits peroxynitrate-mediated tyrosine nitration and peroxynitrate-induced

cytotoxicity, intracellular protein nitration and protein oxidation in human neuroblastoma 8H-SY5Y cells [27].

INTERACTION of H₂S WITH OTHER GASOTRANSMITTER

Gasotransmitters may interact with one another. H₂S, NO and CO facilitate the induction of hippocampal LTP. This effect of H₂S depends on the activation of NMDA receptor whereas that of NO and CO does not. The NO- and CO-induced vasorelaxations are mainly mediated by the cGMP pathway and activation of large conductance K⁺/Ca²⁺ channels in vascular SMCs. Vasorelaxant effects of H₂S is independent on cGMP and K⁺/Ca²⁺ channels as well[16]. Competition for the common hemoglobin sink by one gasotransmitter would potentiate or unmask the biological effect of the other gasotransmitter.

H₂S production in rat aortic tissues is enhanced by NO donor treatment, probably because NO donor also enhances the expression level of CSE in cultured vascular SMCs. Hosoki et al. observed that the vasorelaxant effect of sodium nitroprusside was enhanced by incubation of rat aortic tissues with 30 μM NaHS. On the other side, pretreating aortic tissues with 60 μM H₂S inhibited the vasorelaxant effect of sodium nitroprusside. So, it was hypothesized that H₂S may reduce expression of NOS, decrease sensitivity of cGMP pathway to NO or may modify K⁺/Ca²⁺ channels to decrease their sensitivity to NO. Also, NO may increase cellular uptake of cysteine [16]. So, it requires further studies to know the interaction between NO and H₂S which gives complete picture of regulation of vascular tone.

H₂S was found to be possibly involved in the pathogenesis of hypoxic pulmonary hypertension (HPH). H₂S was significantly decreased in the pathogenesis of HPH. However, plasma CO level and the expressions of heme oxygenase (HO-1) protein and HO-1 mRNA were significantly increased. Exogenous supply of H₂S could alleviate the elevation of pulmonary arterial pressure. At the same time, plasma CO level and the expressions of HO-1 protein and mRNA in pulmonary arteries were significantly increased. Exogenous supply of propargylglycine (PPG), an inhibitor of CSE, decreased the plasma H₂S content and worsened HPH. At the same time, plasma CO level and the expressions of HO-1 protein and mRNA in pulmonary arteries were decreased. The results showed that H₂S could play a regulatory role in the pathogenesis of HPH through up-regulating of CO/HO pathway [28].

Hemoglobin may be the common "sink" for CO in forming scarlet carboxyhemoglobin, for NO in forming nitrosyl hemoglobin, and for H₂S in forming green sulfhemoglobin. If this sink is filled with one gas, the binding of other gases would be affected and their individual availability to act on targeted cells would be altered. After pretreatment of human erythrocytes with CO to saturate the hemoglobin sink, the accumulated amount of endogenous H₂S was significantly enhanced [12].

FUTURE PROSPECTIVE

H₂S may have physiological and pathological role, but still there is long way to go to understand cellular metabolism and function of H₂S. Deficiency in CBS expression causes hyperhomocystinemia, which leads to various diseases. The pathological role of low level of H₂S in such diseases has not been explored. At present, the main therapeutic provision is to supply vitamin B₆, B₁₂ and folic acids. Hydrogen sulfide, another end-metabolic product of homocysteine, obviously reduces homocysteine-induced cardiovascular injury by scavenging oxidative radicals. Increased endogenous or exogenous supply of taurine, hydrogen sulfide and metallothionein might resist cardiovascular injury induced by hyperhomocysteinemia [29]. H₂S promotes glutamate-mediated transmission via NMDA receptors, which might also have implications for neurodegenerative diseases in which excessive activation of NMDA receptors is involved. H₂S level were found to be decreased in patients with Alzheimer's disease; deficiency of SAM might underlie the lack of H₂S in this condition [21]. In Down's syndrome, elevated CBS expression, low plasma homocysteine, and significantly-increased thiosulfate urinary excretion may be associated with abnormally high H₂S levels. These observations led to the hypothesis that accumulation of H₂S in the brain could cause the metabolic intoxication [30]. H₂S is also considered as endogenous vasorelaxant factor. Increased level of H₂S is associated with hypotension [16]. So, abnormal production of H₂S or change in expression of CBS could affect blood pressure. Investigation of molecular interaction between NO and H₂S provides an integrated regulation of vascular tone. Also, molecular mechanism of interaction between H₂S and K⁺ channel require further investigation. H₂S has effect on vascular and pancreatic K⁺ channel without affecting ATP concentration. It was suggested that H₂S may interact with membrane and/or cytosol proteins to form reactive and unstable persulfides. These persulfides may take different forms, including protein-SSH, Thiotaaurine, thiocysteine, thiocystine, or mercaptopyruvate. The persulfide-related sulfuration and structural changes of the targeted proteins are recognized mechanism underlying the interaction of H₂S and K⁺/ATP channel proteins [12]. H₂S inhibit insulin secretion, but on the other hand H₂S is high in insulin resistance condition because of over expression of CBS and CSE. [24, 26] The role of H₂S in both type I and II diabetes needs to be investigated.

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