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REVIEW ARTICLE

H_2S: 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 H_2S, 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. H_2S 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.H_2S induces vasorelaxation, inhibits insulin secretion and also has a role in inflammation. H_2S 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. H_2S 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. H_2S 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 H_2S is produced in various tissues. Recent studies have shown that vascular tissues generate measurable amount of H_2S. High concentration of H_2S has been observed in brain of rats, humans and cows. The H_2S 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 H_2S in brain, but suppress its production in the liver and kidney. H_2S 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 H_2S in the brain. H_2S 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]. H_2S 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-

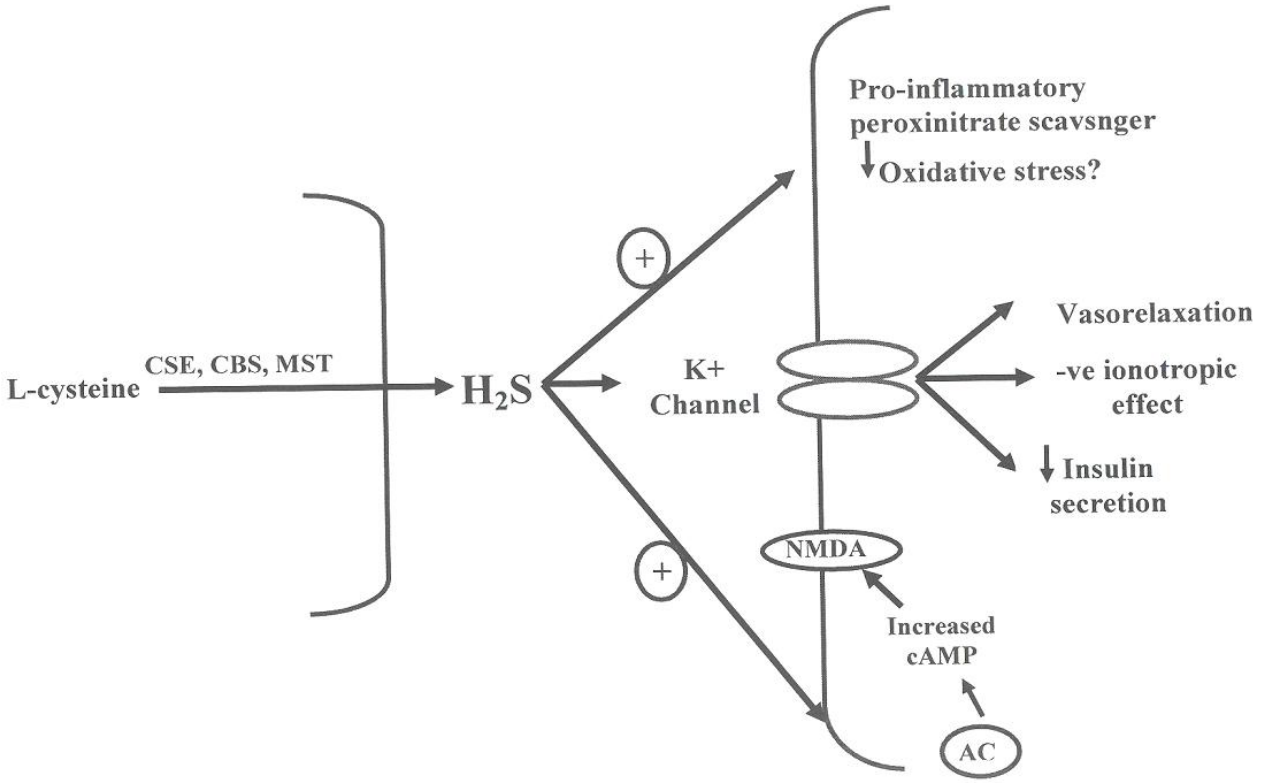

Fig 1. H2S formation and its effect on various conditions in body. CSE:cystathionine gamma lyase, CBS: cystathionine beta synthase, MST:Mercaptopyruvate sulfurtransferase, NMDA: N-methyl-D-aspartate, AC: adenylyl cyclase, cAMP:, cyclic adenosine mono phosphate

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 conformatioal change occurs that frees the catalytic domain and CBS become active. In addition SAM and pyridoxal 5-phosphate, it was recently found that Ca^{2+}/calmodulin-mediated pathways are involved in the regulation of CBS activity. In the absence of Ca^{2+}/calmodulin, the c-terminal domain may cover the catalytic domain and CBS activity remains at a basal level. When Ca^{2+}/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 Ca^{2+}/calmodulin binding sequence, is constantly active, even in absence of Ca^{2+}/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 H_2S 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, H_2S is produced by non-enzymatically reduction of elemental sulfur to H_2S 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].

H_2S CATABOLISM

In vivo, H_2S is metabolized by oxidation in mitochondria or by methylation in cytosol. H_2S can be scavenged by methemoglobin or metallo- or disulfide-containing molecules such as oxidized glutathione. H_2S is excreted mainly by the kidney as free or conjugated sulfate. Thiosulfate is an intermediate in sulfide oxidation to sulfate. Two enymes can act on thiosulfate, namely thiosulfate sulfurtransferase and thiosulfate reductase. One molecule of thiosulfate is formed from two molecules of H_2S [12].

EFFECTS OF H_2S

CARDIOVASCULAR SYSTEM

The presence of H_2S-producing enzyme and endogenous level of H_2S 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 H_2S production in cardiovascular system.

In both in vivo and in vitro experiments, H_2S has negative ionotropic effect on heart. H_2S is considered as endogenous vasorelaxant factor and has a role in the maintaining blood pressure. I.V. bolus injection of H_2S decreases central venous pressure and production of endogenous H_2S. It is essential factor in the development of spontaneous hypertension [13]. Down-regulation of H_2S/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 H_2S may attenuate the process of hypertension. Thus, exogenous H_2S provides a new way for interfering with the progression of hypertension. The hypotensive effect of H_2S was mimicked by pinacidil and antagonized by glibeclamine [15]. It has been shown by Weimin and Wang (2001) that vasorelaxant effect of H_2S is mainly mediated by an interaction of the gas with smooth muscle and partially by functional endothelium [16]. H_2S-induced relaxation of rat aortic tissues was mainly due to direct interaction of H_2S and SMCs, based on the failure of denervation of vascular tissues in vitro to alter H_2S effect and on the observation that H_2S still significantly relaxed vascular tissues after endothelium removal. A small portion of the H_2S-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 H_2S could be explained by the release of endothelium derived vasorelaxant factors in response to H_2S 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 H_2S. It seems that H_2S might release EDHF from vascular endothelium. The presence of an intact endothelium might serve as a buffer to retain H_2S in the blood vessel wall, so that its vasorelaxant effect can be potentiated and prolonged.

Unlike NO and CO, H_2S 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 H_2S. Hypothetically, the interaction between H_2S and ODQ may have generated vasorelaxant free radicals, which further relaxed vascular tissue [16].

The H_2S-induced vasorelaxation is dependant on extracellular entry of Ca^{2+} ions. By directly-acting on vascular SMCs, H_2S may reduce the extracellular calcium entry and relax vascular tissues. Both endothelium and vascular smooth muscles may serve as targets for H_2S. By acting on endothelium, H_2S may facilitate the release of vasorelaxant factors, including NO and EDHF [16]. The most significant vascular effect of H_2S is dependent on K^+/ATP channels. In vascular SMCs, H_2S-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, H_2S 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, H_2S may directly inhibit voltage-gated Ca^{2+} channels in vascular SMCs [16], a possibility that requires further investigation. Hypotension is associated with haemorrhagic shock partly due to the release of endogenous H_2S. Since, H_2S is a vasodilator, it seems likely that overproduction of H_2S during haemorrhagic shock contributes to the hypotension observed [17]. Thus, inhibition of H_2S biosynthesis represents a novel approach to the treatment of haemorrhagic shock, because inhibition of cardiac H_2S biosynthesis might also be expected to improve cardiac output due to negative ionotropic effect of H_2S. It is seen that endogenous vascular H_2S level is increased in rats with septic shock and endotoxic shock. So, it was suggested that endogenous H_2S was involved in pathophysiological process during shock [18]. Deficiency of H_2S may also contribute in pathophysiology of some dieases like atherosclerosis, in some patient with hyperhomocysteinemia, and in whom metabolism of homocysteine to cysteine and H_2S is compromised by vitamine B_6 deficiency [19].

CENTRAL NERVOUS SYSTEM

First evidence for physiological role of H_2S 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 that CSE and based on Northon blot analysis, CBS is the major enzyme for H_2S production in brain [8]. Endogeneous 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 H_2S 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 H_2S was suggested as a probable mechanism. It was also suggested that certain

neuronal effects of H_2S 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].

H_2S also appears to have a role in neuroendocrine fuction because it plays an important role in the control of the hypothalamus-pitutary-adrenal axis. Indeed, increases in H_2S level in hypothalamus either obtained with H_2S-enriched media or by addition of the H_2S 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 importace of H_2S in regulation of neuroendocrine function. NMDA receptors are also target for H_2S, 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 cereballar neurons or in selected rat brain neuronal and glial cell lines. All these observations confirm that H_2S have a role in some aspect of synaptic activity. Also, it was found that H_2S level decreased in patient with Alzheimer's disease. On the other hand, excess of H_2S may lead to mental retardation in patient with Down's syndrome [21], suggesting role of H_2S in CNS disease as a neuromodulator in the brain.

OTHER EFFECTS

H_2S also have other physiological and pathophysiological role in inflammation, diabetes and oxidative stress. Bhatia and co-workers showed the effect of H_2S in inflammatory conditions such as acute pancreatitis. According to their observation, prophylactic and theraputic 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 H_2S in regulating the severity of pancreatitis and associated lung injury. This raises the possibility that H_2S may exert similar activity in other forms of inflammation [23].

H_2S, as a K^+/ATP channel opener, may have effect on pancreatic K^+/ATP channel. H_2S inhibits insulin secretion from pancreatic cell lines and it is high in insulin resistance condition [24]. According to our experiments, H_2S inhibits insulin secretion and its in vivo effect was inhibited by glibeclamide; which proves the effect of H_2S on pancreatic K^+/ATP channel. Streptozotocin-induced diabetes in rats increase expression of CBS and CSE in liver, so H_2S level is also high in that diabetic rats, suggesting role of H_2S in pathophysiology of diabetes [25,26]. H_2S 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 H_2S WITH OTHER GASOTRANSMITER

Gasotransmitters may interact with one another. H_2S, NO and CO facilitate the induction of hippocampal LTP. This effect of H_2S 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^+/Ca^{2+} channels in vascular SMCs. Vasorelaxant effects of H_2S is independent on cGMP and K^+/Ca^{2+} channels as well[16]. Competition for the common hemoglobin sink by one gasotransmitter would potentiate or unmask the biological effect of the other gasotransmitter.

H_2S 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 H_2S inhibited the vasorelaxant effect of sodium nitropruside. So, it was hypothetized that H_2S may reduce expression of NOS, decrease sensitivity of cGMP pathway to NO or may modify K^+/Ca^{2+} channels to decreases 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 H_2S which gives complete picture of regulation of vascular tone.

H_2S was found to be possibly involved in the pathogenesis of hypoxic pulmonary hypertension(HPH). H_2S 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 H_2S 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 H_2S 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 H_2S 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 H_2S 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 H_2S was significantly enhanced [12].

FUTURE PROSPECTIVE

H_2S may have physiological and pathological role, but still there is long way to go to understand cellular metabolism and function of H_2S. Deficiency in CBS expression causes hyperhomocystinemia, which leads to various diseases. The pathological role of low level of H_2S in such diseases has not been explored. At present, the main therapeutic provision is to supply vitamin B_6, B_{12} 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 hyperhomocysteinemi [29]. H_2S promotes glutamate-mediated transmission via NMDA receptors, which might also have implications for neurodegenerative diseases in which excessive activation of NMDA receptors is involved. H_2S level were found to be decreased in patients with Alzheimer's disease; deficiency of SAM might underlie the lack of H_2S I 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 H_2S levels. These observations led to the hypothesis that accumulation of H_2S in the brain could cause the metabolic intoxication [30]. H_2S is also considered as endogenous vasorelaxant factor. Increased level of H_2S is associated with hypotension [16]. So, abnormal production of H_2S 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 H_2S and K^+ channel require further investigation. H_2S has effect on vascular and pancreatic K^+ channel without affecting ATP concentration. It was suggested that H_2S may interact with membrane and/or cytosol proteins to form reactive and unstable persulfides. These persulfides may take different forms, including protein-SSH, Thiotaurine, thiocysteine, thiocystine, or mercaptopyruvate. The persulfide-related sulfuration and structural changes of the targeted proteins are recognized mechanism underlying the interaction of H_2S and K^+/ATP channel proteins [12]. H_2S inhibit insulin secretion, but on the other hand H_2S is high in insulin resistance condition because of over expression of CBS and CSE. [24, 26] The role of H_2S in both type I and II diabetes needs to be investigated.

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