Gaso-transmitter hydrogen sulphide: Potential new target in pharmacotherapy

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Research in the last two decades has transformed the way hydrogen sulphide (H\textsubscript{2}S) is perceived from a noxious gas to a gaso-transmitter with a vast potential in pharmacotherapy. H\textsubscript{2}S is synthesized in various body-systems using the enzymes cystathionine beta-synthase and cystathionine gamma-lyase; either of these being the predominant enzyme in a particular system. H\textsubscript{2}S may be one of the physiological modulators of blood pressure in humans. The gas relaxes the vascular smooth muscle cells by opening up K\textsubscript{ATP} channels. Moreover, it suppresses the proliferation of vascular smooth muscle cells. H\textsubscript{2}S may also be contributing in the protection afforded by ischaemia-preconditioning. Testosterone is thought to be responsible for the higher central nervous system level of H\textsubscript{2}S in males. In the central nervous system, H\textsubscript{2}S is implicated in Alzheimer’s disease, epilepsy, stroke and Down’s syndrome. Insulin secretion is associated with a decrease in the H\textsubscript{2}S levels. Raised H\textsubscript{2}S is detrimental in acute pancreatitis as well as in septic shock. Recently, H\textsubscript{2}S-releasing derivatives of certain drugs have shown promise in protection against gastric ulcer and in inflammatory bowel disease. The beneficial effects of certain sulphur containing herbs like ginseng and garlic may be mediated via H\textsubscript{2}S. In future, development of specific drugs modulating H\textsubscript{2}S levels may prove beneficial in varied disorders.

Keywords: Apoptosis, Cardiovascular system, Gaso-transmitter, Hydrogen sulphide, Nervous system, S-adenosyl-L-methionine

Hydrogen sulphide (H\textsubscript{2}S), a gas with the smell of “rotten eggs”, is known mostly for its noxious effects. It can cause a gamut of deleterious effects in humans and animals when inhaled in more than safe levels. Even when present in a concentration as low as 0.05 ppm, it makes the perceived air quality unpleasant and causes an increase in the anxiety symptoms\textsuperscript{1}. With increasing concentration, it causes irritation of the eyes and the respiratory tract and difficulty in breathing\textsuperscript{2}. Long term exposure to low concentrations may result in fatigue, headache, loss of appetite and decline in cognitive functions\textsuperscript{2}. Even a few breaths of the gas at the concentration of 1000 ppm can prove to be lethal\textsuperscript{3,4}. It is, therefore, not surprising that until two decades ago majority of the studies pertaining to H\textsubscript{2}S were concerned mainly about its toxic potential.

H\textsubscript{2}S: the third gasotransmitter

Around 1990, however, a turning point came for H\textsubscript{2}S. In 1989, endogenous “sulphide” was reported to be present in rat brain tissues and in normal human post-mortem brainstem\textsuperscript{5,6}. These findings suggested endogenous production of H\textsubscript{2}S in the brain. It is now established that H\textsubscript{2}S is produced endogenously in mammals in the brain, blood vessels, liver and kidneys. H\textsubscript{2}S is thought to be implicated in various physiological and pathological processes in humans. It is now being regarded as the third “gaso-transmitter” after NO and CO\textsuperscript{7}. Being a small and lipid soluble molecule, it has the ability to infiltrate the three-dimensional structure of the receptors and affect their functions\textsuperscript{8,9}. This property also makes it easy to pass through biological membranes to exert its effects. Its role is now recognized in various body systems encompassing brain, cardiovascular system, lungs, gastrointestinal tract, liver, kidney and pancreas; and also in inflammation and pain perception\textsuperscript{10}.

Endogenous regulation of H\textsubscript{2}S levels

H\textsubscript{2}S production

Endogenous production of H\textsubscript{2}S is catalysed by two pyridoxal-5-phosphate-dependent enzymes, cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CSE) (Fig. 1). In the brain, H\textsubscript{2}S production is primarily catalyzed by the enzyme CBS using cysteine and homocysteine as substrates\textsuperscript{4}.

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CBS is highly expressed in the brain while CSE mRNA levels are undetectable in the brain using northern blot analysis. Also, S-adenosyl-L-methionine (SAMe), the allosteric activator of the enzyme CBS, increases while CBS inhibitors hydroxylamine and amino-oxyacetate decrease the brain H\(_2\)S levels. On the other hand, CSE inhibitors D,L-propargylglycine and \(\beta\)-cyano-L-alanine had no effect on the brain H\(_2\)S levels\(^{11}\). In the cardiovascular system, however, CSE is the major enzyme responsible for H\(_2\)S production, catalyzing the conversion of cystine to cysteine, H\(_2\)S, NH\(_3\) and pyruvate\(^{12,13}\). Recently, another enzymatic pathway of H\(_2\)S synthesis has been identified. 3-Mercaptopyruvate sulphur transferase (3MST) in conjunction with cysteine aminotransferase (CAT) can produce H\(_2\)S from cysteine in the presence of \(\alpha\)-ketoglutarate. 3MST has been found to be localized to neurons as well as to vascular endothelium and smooth muscle cells\(^{14}\). However, the physiological significance of this pathway is not yet completely known\(^{15}\).

**Regulation of H\(_2\)S production**

There appear to be at least three ways in which the endogenous production of H\(_2\)S is regulated\(^{16}\). The first is neuronal excitation which is responsible for the “fast regulation” of H\(_2\)S. This fast regulation is mediated via Ca\(^{2+}\)/Calmodulin. In presence of Ca\(^{2+}\) and calmodulin, the rate of production of H\(_2\)S by CBS is increased 3.5-times than that in their absence. Also, trifluoroperazine and W-13, two inhibitors of calmodulin, result in suppression of H\(_2\)S production\(^{17}\). A “slower” pathway regulating the endogenous H\(_2\)S levels was found to be controlled by testosterone. The idea that sex hormones could play a role in H\(_2\)S production came into being after the finding that endogenous H\(_2\)S levels in the brains of male mice were higher as compared to that of the females\(^{16}\). To test the hypothesis, Eto et al.\(^{17}\) conducted a series of experiments. After a single administration of testosterone, the brain H\(_2\)S levels of female mice almost reached the levels that of male mice. The results were further consolidated when castration of male mice resulted in a decrease in the testosterone
levels accompanied by a decrease in brain H$_2$S levels. In both the experiments, there were no significant changes in the brain CBS levels suggesting that testosterone increases the H$_2$S levels in the brain by increasing only the “activity” of the enzyme CBS. This increased activity of the enzyme was subsequently found to be mediated via SAMe. Thus, it could be concluded that SAMe is the downstream effector responsible for the changes in brain H$_2$S levels induced by testosterone$^{16}$. However, it was observed that the difference in the brain H$_2$S levels was not as great as the difference in the brain testosterone levels. Also, the age-related changes in the testosterone levels did not correlate well with the brain H$_2$S levels. This suggested that there could be some additional pathway(s) that control the basal H$_2$S levels. It is hypothesized that glucocorticoids might regulate this third pathway as they have been found to regulate SAMe synthesis in the liver.$^{16}$.

**Catabolism of H$_2$S**

H$_2$S does not accumulate in the body and is rapidly metabolized. Sulphate is the major end product and is excreted in urine. Thiosulphate, another by-product of H$_2$S metabolism, is also excreted in the urine and although present in low concentration, it serves as the biomarker of H$_2$S metabolism$^{18}$.

**Role of H$_2$S in the cardio-vascular system**

**Hypotensive effect**

The role of H$_2$S in the cardiovascular system has been studied in relative detail. It is thought to be implicated in an array of pathophysiological conditions. Interestingly, the hypotensive effects of garlic and other sulphur-containing natural substances, like onions and mushrooms, may be mediated via H$_2$S$^{12}$. Similar to the other two gasotransmitters, namely, NO and CO, H$_2$S also relaxes the vascular smooth muscle cells. H$_2$S, however, differs from NO and CO, in that the vasorelaxant effect is not mediated via cGMP. H$_2$S is thought to act by opening up of K$_{ATP}$ channels present on the vascular smooth muscle cells$^{19-21}$. This causes membrane hyperpolarization with resultant relaxation of vascular smooth muscle cells$^{13}$. The probable role of H$_2$S in hypertension has been studied in animal model of spontaneous hypertension. Exogenous administration of H$_2$S donor sodium hydrogen sulphide (NaHS) in spontaneously hypertensive rats could alleviate hypertension and help recover the suppressed plasma H$_2$S levels and CSE activity$^{22}$. The effect of H$_2$S on the vascular resistance is not limited to its vasorelaxant property. H$_2$S is also thought to prevent the development of hypertension by suppressing the proliferation of vascular smooth muscle cells and by accelerating their apoptosis via mitogen-activated protein (MAP) kinase pathway$^{23,24}$. These findings suggest that H$_2$S may be one of the mediators in the regulation of blood-pressure.

**Cardioprotective effect**

H$_2$S has also been reported to possess cardioprotective effect$^{19,21,25}$. Ischaemia-preconditioning of heart (subjecting the tissue to multiple brief periods of ischaemia) protects against myocardial damage caused by actual ischaemia$^{26}$. This protective effect was observed to be abolished by treatment with CSE inhibitors DL-proparglyglycine or β-cyano-L-alanine. The protection is restored when the H$_2$S donor NaHS is co-administered. Thus, H$_2$S seems to be responsible for the protection achieved by ischaemia preconditioning. This was further substantiated by the fact that ischaemia causes a significant decrease in the H$_2$S levels in cultured cardiac myocytes, an effect which is attenuated by ischaemia-preconditioning and pretreatment with NaHS$^{19}$. In addition, NaHS has been shown to offer protection against myocardial infarction in an animal model$^{27,28}$. Recently, the protective effect of H$_2$S against regional myocardial ischaemia/reperfusion injury was shown to be due to the gas’s anti-apoptotic and anti-inflammatory effects$^{29}$. H$_2$S is also thought to be involved in several other cardiovascular pathologies like hypoxia-induced pulmonary hypertension$^{30}$, high blood flow induced pulmonary hypertension$^{31}$, cystathioninuria$^{27}$ and septic and endotoxic shock$^{32}$.

**Role of H$_2$S in the central nervous system**

**Neuromodulator role**

Following reports that high levels of H$_2$S are present in the brain$^{5,6,33}$, the physiological function of H$_2$S was explored. It was observed that H$_2$S facilitates the long-term potentiation (LTP) in the hippocampus. This induction of LTP was not seen in the presence of 2-amino-S-phosphonovalerate, an NMDA receptor antagonist indicating that H$_2$S requires activation of NMDA receptors for the induction of hippocampal LTP$^{31}$. This is in contrast to CO and NO that can induce LTP even when the NMDA receptors are blocked$^{34}$. Also, H$_2$S could facilitate LTP only in
active synapses suggesting its role in associative learning and as a neuromodulator. Further investigating the role of H$_2$S in synaptic activity, Eto et al. found that absence of H$_2$S in CBS knock-out mice altered the LTP in hippocampal slices.

H$_2$S has been shown to reduce the potassium-stimulated release of corticotrophin releasing hormone by rat hypothalamus. Also, H$_2$S attenuates the hypothermia-induced glucocorticoid release, implicating the role of H$_2$S in the negative feedback of the hypothalamo-pituitary-adrenal axis. These observations imply an important role of H$_2$S in neuromodulation.

**Role in Alzheimer’s disease**

Alzheimer’s disease (AD) is a neurodegenerative disease of increasing public health importance. Although several risk factors have been found to be associated with an increased incidence of AD, the exact mechanism of disease causation is still to be unravelled. Increased oxidative stress due to free radicals has been proposed as one of the potential mechanisms for the development of AD. In fact, oxidative stress has been found to be linked to “neurofibrillary tangle”, a major pathological finding in AD.

Interestingly, the levels of H$_2$S in AD brains have been found to be significantly lower than in the normal post-mortem brains. This is associated with low levels of SAMe, thus suggesting decreased activity of the enzyme CBS in AD brains. It has been shown that decreased levels of H$_2$S result in inefficient scavenging of oxidising species like peroxynitrite and hypochlorous acid resulting in neuronal damage, intracellular protein oxidation and lipid peroxidation thereby contributing to the pathogenesis of AD.

Of late, disturbance in the cerebral microvasculature, resulting in cerebral ischaemia, has also been linked to the pathogenesis of AD. H$_2$S may be involved in this pathway as well, considering its role in vascular relaxation. Finally, the role of H$_2$S as a facilitator of long term potentiation in the hippocampus may also be implicated in the cognitive compromise encountered in AD.

**Role in epilepsy**

Human studies have found hippocampal damage to be an important feature of recurrent febrile seizures. Following the reports of high expression of CBS in the hippocampus and potential neuromodulatory role of H$_2$S, Han et al. studied the role of H$_2$S in animal model of recurrent febrile seizures using sodium hydrogen sulphide as a donor of H$_2$S. High levels of H$_2$S could inhibit synaptic transmission in the hippocampus preventing the neurons from excitatory toxicity. Also, H$_2$S could down-regulate c-fos during the development of febrile seizures and prevents mossy fibre sprouting, indicating neuronal protection.

American ginseng root is known to contain 0.15 % sulphur. The effect of a closely related ginseng — *Panax ginseng* was studied in pentylenetetrazole-induced kindling in rats. *Panax ginseng* group showed significantly higher protection as compared to the vehicle group. Though the exact mechanism of antiepileptic activity of *Panax ginseng* has not been elucidated, partial involvement of H$_2$S cannot be ruled out considering the sulphur content of the herb. Further research in this direction is warranted.

Dahiya et al. suggested a protective role of SAMe against pentylenetetrazole (PTZ)-induced seizures in rats. Adult male Wistar weighing 180-240 g were divided into three groups of six each. PTZ was administered to each group in a dose of 60 mg/kg, ip to induce seizures. All the animals in group 1 (negative control) experienced generalized tonic-clonic (GTC) seizures. Group 2 (positive control) animals were pretreated with valproic acid (300 mg/kg, ip) 30 min prior to PTZ administration. None of the animals in this group experienced seizures. Animals in group 3 (SAMe) were administered SAMe (400 mg/kg/day, po) for three days before PTZ administration. PTZ was administered on the third day, 90 min after the last dose of SAMe. Three out six animals in this group did not experience GTC seizures. The other three animals who did experience seizures had significantly increased latency to GTC, indicating protective effect of SAMe against seizures induced by PTZ.

SAMe is known to increase the levels of H$_2$S by increasing the activity of the enzyme CBS. Eto and Kimura reported that administration of SAMe once a day for three days causes brain H$_2$S levels to be significantly increased. Conversely, decreased activity of SAMe has been related to decreased levels of H$_2$S. Additionally, H$_2$S donor sodium hydrogen sulphide has been shown to be protective against hippocampal damage produced by recurrent febrile seizures in rats by raising brain H$_2$S levels. Thus, it is possible that...
the protection afforded against seizures\textsuperscript{43} may be due to raised brain H\textsubscript{2}S levels after the administration of SAMe. Further research, aimed at estimation of brain H\textsubscript{2}S levels and their correlation with seizure-protection is, however, needed to consolidate this hypothesis.

**Deleterious effect of H\textsubscript{2}S on central nervous system**

There is some evidence of deleterious effects of H\textsubscript{2}S in the CNS too. CNS levels of H\textsubscript{2}S have been found to be increased in Down’s syndrome (trisomy of chromosome 21). Intriguingly, the gene encoding CBS is located on chromosome 21 at the position 22.3\textsuperscript{44}. Excess of H\textsubscript{2}S in Down’s syndrome is thought to cause neuronal damage via inhibition of cytochrome c oxidase or overstimulation of NMDA receptors\textsuperscript{45}. Apart from this, detrimental effect of H\textsubscript{2}S has been seen in middle cerebral artery occlusion model of stroke\textsuperscript{46}. It was found that administration of NaHS, an H\textsubscript{2}S donor, before permanent occlusion of the middle cerebral artery, increased the infarct size. On the other hand, various inhibitors of H\textsubscript{2}S production decreased the infarct volume. The inhibitors of the enzyme CBS (amino-oxyacetate and hydroxylamine) were found to have a greater protective effect than the inhibitors of CSE (β-cyano-L-alanine and DL-propargylglycine) which is in concordance with the fact that CBS is the major enzyme catalyzing the formation of H\textsubscript{2}S in the brain. It was also noted that the protective effect was directly proportional to the potency of the inhibitors to decrease H\textsubscript{2}S production in vitro\textsuperscript{46}.

**Other roles of H\textsubscript{2}S**

**Systemic and local inflammation**

The vasodilator action of H\textsubscript{2}S suggests its potential role in inflammation. This was proved in several studies in which inflammation was induced locally or systemically in animals. H\textsubscript{2}S levels were found to increase in both septic and endotoxic shock along with an increase in nitric oxide level. The levels of H\textsubscript{2}S were found to be negatively correlated with the blood pressure and cardiac function\textsuperscript{47}. It was found that H\textsubscript{2}S is increased in experimental model of pancreatitis\textsuperscript{48,49}. That H\textsubscript{2}S was not just an accompanying feature of pancreatitis but was involved in its causation was inferred from the fact that administration of DL-propargylglycine not just inhibited H\textsubscript{2}S production but also attenuated the severity of pancreatic inflammation and the lung injury that accompanies severe pancreatitis. Though the pancreatic-inflammation and the associated oedema could be explained by the vasodilator property of H\textsubscript{2}S, acinar-cell necrosis could not. It was proposed that H\textsubscript{2}S produced locally could activate thezymogens initiating the autodigestive process\textsuperscript{48}.

**Insulin release**

Insulin release from pancreatic β-cells is thought to be regulated via K\textsubscript{ATP} channel. When the extracellular level of glucose is low, K\textsubscript{ATP} channels are open keeping the β cell hyperpolarized. With increasing concentration of glucose, a series of events takes place causing inhibition of K\textsubscript{ATP} channel. This causes increase in membrane electric potential resulting in opening up of voltage-sensitive Ca\textsuperscript{2+} channels. Raised intracellular Ca\textsuperscript{2+} finally results in release of insulin from storage granules. Sulfonylureas, like glucose, cause insulin secretion by blocking K\textsubscript{ATP} channel\textsuperscript{50}.

Considering the fact that H\textsubscript{2}S causes relaxation of vascular smooth muscle cells via opening up of K\textsubscript{ATP} channels, it is logical to envisage that the gas might as well affect K\textsubscript{ATP} channels in pancreatic β cells, although molecular composition of K\textsubscript{ATP} channels is different among different cell types. To test this possibility, the effect of H\textsubscript{2}S was studied on INS-1E cells derived from insulinoma pancreatic β-cell line. INS-1E cells were found to produce significant amounts of H\textsubscript{2}S, mainly via CSE enzyme. At low concentration of extracellular glucose, H\textsubscript{2}S level is high, keeping the β cell hyperpolarized. Increasing the level of extracellular glucose could inhibit H\textsubscript{2}S production causing membrane depolarization resulting in insulin release. The fact that H\textsubscript{2}S production is regulated by extracellular glucose concentration implies that H\textsubscript{2}S could be one of the physiological regulators of insulin secretion in humans\textsuperscript{51}.

**Renal ischaemia-reperfusion injury**

Analogous to its protective effect against ischemia-reperfusion (I/R) injury to the heart, H\textsubscript{2}S has shown to improve the outcome of I/R in porcine model of non-heart-beating donor kidneys\textsuperscript{52}. In brief, the kidneys were subjected to 25 min of warm ischaemia followed by 18 h of cold storage. They were then reperfused ex vivo with autologous blood. In one group, H\textsubscript{2}S donor sodium hydrogen sulphide was administered 10 min before and after reperfusion, while in the other group (control), no such treatment was given. It was observed that, H\textsubscript{2}S caused significant improvement in
the markers of kidney function. Renal blood flow improved significantly as compared to the control group attributable to the vasodilation caused by H\textsubscript{2}S. This was associated with reduced oxidative damage, lower serum creatinine levels, greater creatinine clearance and higher urine output in the H\textsubscript{2}S-treated group. The finding, thus, indicates potential role of H\textsubscript{2}S in kidney transplant recipients\textsuperscript{37}.

**Apoptosis**

Apoptosis is a process of programmed cell death in response to appropriate trigger. The mitogen-activated protein kinases (MAPK) superfamily, consisting of extracellular signal-regulated kinase (ERK), p38 MAPK and c-Jun N-terminal kinase (JNK), plays an important role in cell survival and apoptosis\textsuperscript{53}. Both pro-apoptotic and anti-apoptotic actions of H\textsubscript{2}S have been identified in different situations. Yang et al.\textsuperscript{24} demonstrated that physiological concentrations of H\textsubscript{2}S induce apoptosis of human aorta smooth muscle cells. They further proved that this action of H\textsubscript{2}S was via the activation of ERK and was associated with increased concentrations of caspase-3, an important executioner of apoptosis\textsuperscript{24}. On the other hand, in ischaemia/reperfusion model, sodium hydrogen sulphide, a donor of H\textsubscript{2}S, was found to oppose apoptosis by preventing the activation caspase-9. Sodium hydrogen sulphide also ameliorated the decreased expression of Bcl-2, an anti-apoptotic protein, caused by ischaemia/reperfusion. It was shown that these anti-apoptotic effects of sodium hydrogen sulphide could be mediated via opening up of putative mitochondrial K\textsubscript{ATP} channels\textsuperscript{29}. In another study, sodium hydrogen sulphide concentration-dependently suppressed rotenone-induced apoptosis in human-derived dopaminergic neuroblastoma cell line. This finding has implications in the therapy of neurodegenerative diseases like Parkinson’s disease\textsuperscript{54}. Recently, sodium hydrogen sulphide has shown to protect the H9c2 embryonic rat cardiac cells against cobalt chloride-induced injury. The effect was attributed to the ability of H\textsubscript{2}S to attenuate inflammation and suppress caspase-3 activation, thereby preventing apoptosis\textsuperscript{55}.

The proapoptotic effect of H\textsubscript{2}S indicates its potential antineoplastic action. In fact, H\textsubscript{2}S, at physiological concentration, has been shown to decrease the viability of colon cancer cells\textsuperscript{56}. The antineoplastic effects of garlic have been attributed to its sulphur content\textsuperscript{57}. In various animal studies, consumption of garlic has been shown to have a protective effect against tumours of the gastrointestinal tract, mammary glands, skin and liver\textsuperscript{58-62}. However, there is also some evidence suggesting a mutagenic potential of H\textsubscript{2}S\textsuperscript{63}. Further studies are required to explain the controversy.

**H\textsubscript{2}S: future prospects and unresolved issues**

In concordance with the vasodilator property of H\textsubscript{2}S, NaHS, a precursor of H\textsubscript{2}S, was shown to improve penile length and cavernous pressure in primates. DL-propargylglycine, on the other hand, had an opposite effect by inhibiting H\textsubscript{2}S formation\textsuperscript{64}. Thus, in future, therapy of erectile dysfunction may include modulation of H\textsubscript{2}S release.

Present modulators of H\textsubscript{2}S levels are non-specific\textsuperscript{65} and thus their use is limited to research only. However, a few drugs, chemically modified to release H\textsubscript{2}S, are being tested for their additional benefit\textsuperscript{66}. “H\textsubscript{2}S-releasing derivatives” of non-steroidal anti-inflammatory drugs (NSAIDs) diclofenac and indomethacin have been found to cause significantly less gastric hemorrhagic lesions and leucocyte adherence than the “original drugs”\textsuperscript{67}. Leucocyte adherence to the vascular endothelium of the mesenteric circulation was linked with the NSAID-induced gastric damage\textsuperscript{67}. In addition, H\textsubscript{2}S-releasing derivative of mesalamine has been shown to decrease the inflammation associated with inflammatory bowel disease\textsuperscript{68}. H\textsubscript{2}S has also shown analgesic effect on visceral pain which is a troublesome feature of inflammatory bowel disease\textsuperscript{69}. There is evidence that this anti-nociceptive effect is mediated via K\textsubscript{ATP} channels\textsuperscript{70}.

The role of H\textsubscript{2}S in nociception is, however, not well-defined. H\textsubscript{2}S has been shown to increase the neutrophil migration at the site of inflammation. This is thought to cause increased nociception by increasing PGE\textsubscript{2} production\textsuperscript{71}. On the other hand, exogenously increasing the H\textsubscript{2}S in colorectal distension-induced nociception model in rats has shown anti-nociceptive property via activation of K\textsuperscript{ATP} channels\textsuperscript{69,70}. These controversial results could be because of the difference in the H\textsubscript{2}S concentration achieved by endogenous and exogenous routes\textsuperscript{72}.

Keeping in view the wide ranging effects of H\textsubscript{2}S, (Fig. 2) discovery of suitable modulators of its levels in future may open new avenues of treatment options in a variety of diseases like hypertension, Alzheimer’s disease, Down’s syndrome, inflammatory conditions...
like inflammatory bowel disease, septic shock and acute pancreatitis, various neoplasms and erectile dysfunction. Also, the effects of various sulphur-containing herbs like garlic and ginseng may be mediated via H$_2$S. Further research is thus required to fully realize the potential of H$_2$S.

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