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THEME | *Gaso-Transmitters*

Vascular biology of hydrogen sulfide

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[1]*Vascular Physiology Group, Department of Cell Biology and Physiology, School of Medicine, University of New Mexico, Albuquerque, New Mexico;* [2]*Department of Anesthesiology, University of Texas Medical Branch, Galveston, Texas;* [3]*Laboratory of Pharmacology, Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece; and* [4]*Center of Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece*

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Kanagy NL, Szabo C, Papapetropoulos A. Vascular biology of hydrogen sulfide. *Am J Physiol Cell Physiol* 312: C537–C549, 2017. First published February 1, 2017; doi:10.1152/ajpcell.00329.2016.—Hydrogen sulfide (H_2S) is a ubiquitous signaling molecule with important functions in many mammalian organs and systems. Observations in the 1990s ascribed physiological actions to H_2S in the nervous system, proposing that this gasotransmitter acts as a neuromodulator. Soon after that, the vasodilating properties of H_2S were demonstrated. In the past decade, H_2S was shown to exert a multitude of physiological effects in the vessel wall. H_2S is produced by vascular cells and exhibits antioxidant, antiapoptotic, anti-inflammatory, and vasoactive properties. In this concise review, we have focused on the impact of H_2S on vascular structure and function with an emphasis on angiogenesis, vascular tone, vascular permeability and atherosclerosis. H_2S reduces arterial blood pressure, limits atheromatous plaque formation, and promotes vascularization of ischemic tissues. Although the beneficial properties of H_2S are well established, mechanistic insights into the molecular pathways implicated in disease prevention and treatment remain largely unexplored. Unraveling the targets and downstream effectors of H_2S in the vessel wall in the context of disease will aid in translation of preclinical observations. In addition, acute regulation of H_2S production is still poorly understood and additional work delineating the pathways regulating the enzymes that produce H_2S will allow pharmacological manipulation of this pathway. As the field continues to grow, we expect that H_2S-related compounds will find their way into clinical trials for diseases affecting the blood vessels.

hydrogen sulfide; signaling; endothelium; vascular smooth muscle; blood vessels

HYDROGEN SULFIDE (H_2S) is a ubiquitous second messenger molecule with important functions in the vessel wall (75, 161). Three enzymes have been shown to enzymatically generate H_2S, cystathionine β-synthase (CBS), cystathionine γ-lyase (CTH or CSE) and 3-mercaptopyruvate sulfurtransferase (3MST) (85, 108, 158). CBS and CSE participate in the interconversion of homocysteine to cysteine, known as the transsulfuration pathway; both enzymes are pyridoxal-5 phosphate dependent (70, 75). It should, however, be kept in mind that CBS and CSE catalyze a number of additional reactions that do not yield H_2S (70). CBS possesses unique features: it is the only known PLP-dependent enzyme with a heme prosthetic group and has a positive allosteric activator, *S*-adenosylmethionine (70). Under resting conditions, in many cell types, CBS and 3MST are found in both the mitochondria and the cytosol (132, 145, 153), while CSE is only present in the cytosol (48, 153).

All three H_2S-producing enzymes have been reported to be expressed in vascular cells (115, 126, 131). However, little is known about the molecular pathways regulating their expression in vascular cells. Reactive oxygen species and laminar shear flow have been shown to enhance the expression of CSE and 3MST (61, 104), respectively, while elevations in calcium and specificity protein 1 (Sp1) have been shown to upregulate CSE in smooth muscle cells (165, 179). The majority of the vascular studies have focused on CSE. One factor that has contributed to this is the availability of better pharmacological inhibitors for CSE (116). Moreover, although CBS-deficient mice were available years before CSE knockouts (167), their severe phenotype resulting in death in the first weeks of life has limited their usefulness in experimental studies, leading investigators to use heterozygotes (2, 18, 106). In contrast, CSE knockout mice have no developmental abnormalities and appear to have a normal lifespan; they do, however, display a cardiovascular phenotype with elevated blood pressure and reduced endothelial-dependent responses (183). Although 3MST mice are available, no data have been published on their cardiovascular characteristics (110).

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Acute vs. Delayed Effectors and Pathways in H_2S Signaling

Hydrogen sulfide is highly soluble in water with a solubility of 80 mM at body temperature (71). It is also soluble in lipid membranes so that it has access to both intracellular and extracellular sites of target proteins (99, 122). Because H_2S is a weak acid, it equilibrates with its anion HS^- at body temperature (pK_a of 7) with ~70% being present as HS^- at physiological pH (103). The chemical nature of the molecule(s) responsible for the biological activity of H_2S remains elusive; H_2S itself, HS^-, polysulfides, as well as S/N hybrid species have been shown to affect a variety of signaling pathways leading to biological responses (38, 76, 85, 87, 112). The targeted pathways include kinases and phosphatases, additional enzymes, ion channels, and transcription factors (Fig. 1). A primary mechanism through which H_2S affects the activity of signaling proteins is persulfidation of reactive cysteine residues on target proteins to form a persulfide group (–SSH) (117, 127). Depending on the nature of the targeted protein, the effects of H_2S might take from seconds to days to manifest. For example, persulfidation of ATP-sensitive (K_{ATP}) channels leads to hyperpolarization and relaxation of smooth muscle cells that occurs within seconds, while persulfidation of Keap-1 (185) allows activation of Nrf-2 and enhanced antioxidant gene expression, requiring hours to days for biological effects to become apparent.

One of the earliest demonstrations of H_2S sulfhydryl modification of cysteine residues leading to a functional change was a report by Mustafa et al. (107) that persulfidation on Cys150 augments glyceraldehyde dehydrogenase (GAPDH) activity. This study found that up to 25% of the proteins in liver homogenates were endogenously persulfidated, suggesting that sulfhydration is a widespread signaling paradigm. However, several years later Jarosz and coworkers were not able to reproduce the activation of GAPDH by persulfidation and instead observed a decrease in enzyme activity after modification of the protein by H_2S (67a). Thus, the role of H_2S modification of GAPDH in regulating cellular function is still unclear.

More recently, persulfidation of other targets has also been linked to changes in function. Persulfidation of inositol trisphosphate receptors (IP_3R) was shown to inhibit Ca^{2+} release through these receptor channels, leading to H_2S-induced airway relaxation (29). H_2S modification of the mitogen activated protein kinase, MEK1, improved DNA damage repair and decreased senescence through PARP-1 activation (193). Both K_{IR} and IK_{Ca} potassium channels (109), mitochondrial proteins (35, 140, 147), cytochrome P_{450} enzymes (164), NF-κB (128), and PTEN (111) have also been identified as targets of sulfhydration, suggesting that there is indeed widespread cellular regulation through this modification. For the majority of these modifications, persulfidation is inhibitory but there are notable exceptions including the early report by Mustafa et al. (107) for GAPDH and more recent descriptions of increased MEK1 activity after persulfidation in human umbilical vein endothelial cells (HUVECs; 193).

Evidence for the critical role of persulfidation in H_2S signaling is largely dependent on observations that reversal of persulfide formation with dithiothreitol or another reducing agent reverses the effects of H_2S treatment (29, 192). In addition, cysteine mutation studies further suggest that the H_2S targets cysteine residues including Cys341 in MEK1 as the mediator of H_2S-induced ERK1/2 phosphorylation and translocation (193) or Cys139 in the activation of PPAR-γ activity and translocation to the nucleus (25). In this latter study, mice fed a high-fat diet were protected from developing insulin resistance and liver injury by administration of a H_2S donor, suggesting that H_2S is protective from metabolic effects of a high-fat diet. Intriguingly, a high-fat diet downregulates the expression of CSE (51) and post hoc analysis of urinary sulfate concentrations in type 2 diabetic patients demonstrated a strong

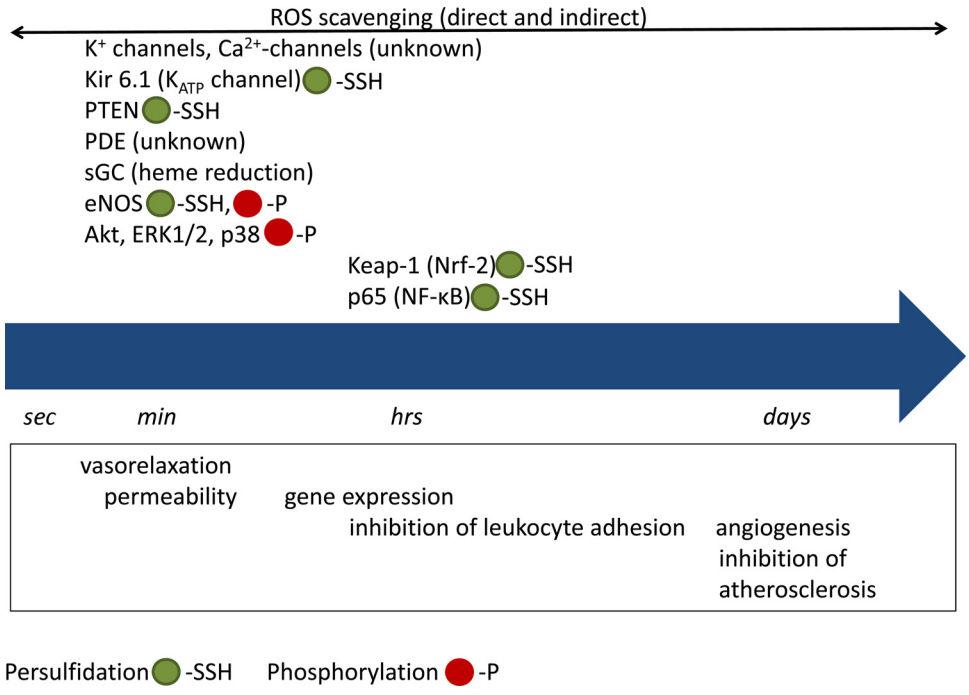

Fig. 1. Timescale of H_2S effects. Acute effects of H_2S include activation/inhibition of ion channels, kinases, and other enzymes. These events are observed within a few seconds and up to several minutes after exposure to H_2S. Chronic effects are dependent on gene expression and involve altered transcription factor activity; although activation/inhibition of transcription factors might be observed within minutes to hours after H_2S administration, the biological effects are not observed until after much later, requiring up to days to manifest. It should be noted that phosphorylation is secondary to activation of a kinase or inhibition of a phosphatase, through persulfidation or other mechanisms.

correlation with estimated glomerular filtration rate (eGFR), suggesting that renal H_2S production is associated with protection from renal consequences of diabetes (155).

Persulfidation can be reversed by the thioredoxin system (168). Of interest, the thioredoxin system is upregulated in patients with sleep apnea (148) suggesting that upregulation of thioredoxin could modify H_2S-regulated pathways during sleep apnea or other states of high oxidative stress. A recent study observed that thioredoxin cleavage of persulfide moieties leads to the release of H_2S, suggesting that the persulfidated proteins could be an endogenous source of free H_2S in the circulation (168).

The NO/cGMP pathway represents another major signaling mechanism through which H_2S exerts its biological effects (16). H_2S was shown to inhibit PDE activity and increase cGMP in smooth muscle cells (22). Additional ways through which H_2S can affect the NO/cGMP pathway include *1*) enhanced phosphorylation of the activator site S1177 of eNOS (36), *2*) stabilization of eNOS in its dimeric active form (6), and *3*) regulation of soluble guanylate cyclase (sGC) redox state shifting sGC towards the ferrous, NO-responsive form (200). Although, the effects of H_2S on sGC and phosphodiesterase type 5 (PDE5) occur in the absence of persulfidation (16, 200), H_2S-stimulated eNOS dimerization is mediated by persulfidation of C443 (6).

Vascular Tone

The primary action of H_2S in the vasculature is vasodilatory (74, 85, 161) (Fig. 2). However, biphasic responses to H_2S have been reported (40, 151). In addition, conflicting reports on the site and the vasorelaxant mechanism of action of H_2S in the vasculature demonstrate that there is heterogeneity in the vascular responses to H_2S. It is possible that much of the inconsistent data in the literature is due in part to species differences; more studies are needed to resolve the existing discrepancies.

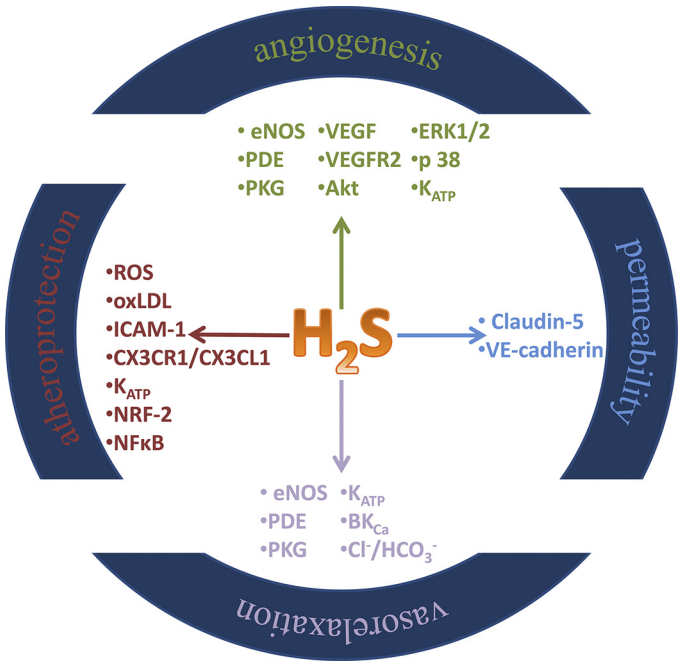

Fig. 2. Summary of biological activity of H_2S in vascular cells.

The earliest reports on vasoactive responses to endogenous H_2S were from the laboratory of Hideo Kimura, who demonstrated in 1997 that several types of smooth muscle including aortic smooth muscle cells express H_2S-synthesizing enzymes and generate H_2S (60). This study also observed that relaxation of smooth muscle by H_2S donors in rats was augmented in the presence of NO and H_2S supplementation increased the dilatory response to NO donors. Based on its interaction with NO, one would expect that endothelium removal would reduce H_2S-induced relaxation; however, several reports have shown that endothelial denudation does not significantly alter H_2S responses (23, 60). Later studies, from Rui Wang's group demonstrated the importance of K_{ATP} for H_2S-triggered vasorelaxation (195). Based on *1*) its ability to hyperpolarize endothelial and smooth cell membranes, *2*) its biological activity on small and/or intermediate conductance K_{Ca} channels, and *3*) its greater potency as a vasodilator in resistance versus conduit arteries, H_2S has been proposed as a candidate for the elusive endothelium-derived hyperpolarizing factor (11, 109, 151).

Activation of K_{ATP} channels in isolated arteries from multiple species (89, 92, 109, 133) and in dissociated mouse colonic or rat cardiac myocytes (49, 199) requires millimolar concentrations of H_2S donors, while endogenous levels of H_2S are consistently reported in nanomolar (130) to micromolar (129) levels. In addition, infusion of H_2S into a perfused mesenteric bed (31) or isolated porcine cerebral arteries (82, 89) causes dilation that is only partially inhibited by glibenclamide. In rat thoracic aorta, H_2S at high micromolar concentrations caused vasorelaxation that was unaffected by the K_{ATP} channel blocker glibenclamide; this effect was reduced by a Cl^-/HCO_3^- channel inhibitor and was associated with an overall metabolic suppression of the vascular tissue (77). Several groups have reported that nanomolar to micromolar concentrations of H_2S activate large conductance Ca^{2+}-activated potassium channels (BK_{Ca}) (63, 134) and the voltage-gated potassium channels (58, 95). A study in bovine retinal arteries demonstrated that the relaxation in response to the H_2S donor NaHS was insensitive to K_{ATP} inhibition, but partially blocked by inhibition of K_V and K_{IR} inhibition (150). The physiological significance for H_2S-induced dilation for some of the above-mentioned pathways remains unclear and there may be important species differences.

Other pathways implicated in H_2S dilation include activation of nitric oxide synthase (NOS) and cyclooxygenase in human microvessels (81). Work in rodent vessels demonstrated that dilation to sulfide salts is attenuated in vessels from endothelial (e)NOS knockout (KO) mice (36). In line with the ability of NaHS and Na_2S to increase cGMP levels in rodent smooth muscle cells (22, 23), Bucci et al. (23) demonstrated that sulfide salt-induced relaxations in mouse aorta were inhibited by DT-2, a cGMP-dependent protein kinase I (PKG-I) inhibitor, and in PKG-I KO animals. However, not all H_2S donors cause vasodilation using the NO/cGMP pathway. For example, vasorelaxing responses in the bovine ciliary artery to the slow-releasing H_2S donor compound GYY4137 were not blocked by nitro-L-arginine methyl ester (L-NAME; 34) and relaxations to the same H_2S donor were not inhibited by DT-2 in the mouse aorta (23). Therefore, both exogenous and endogenous H_2S can activate multiple second messenger sys-

tems, leading to relaxation of vascular smooth muscle. The pathways utilized seem to depend on the vascular bed studied, the species examined, and on the H_2S source used.

Under certain conditions, H_2S has also been found to enhance contraction of smooth muscle. In the rat mesenteric arterial bed, lower concentrations of H_2S (up to 100 μM) promoted contraction, while higher concentrations elicited relaxations (40). Similar observations, with lower H_2S concentrations eliciting contractions and higher concentrations exhibiting vasorelaxation, have been observed in the mouse aorta (151) and the rat gastric artery (80). In rat basilar arteries, Li and coworkers (88) observed vasoconstriction to NaHS at concentrations of 1.0 to 150 μM that was prevented by inhibition of adenylyl cyclase. The above studies, taken together, suggest that experimental and preexisting conditions influence the final functional response to increases in H_2S. Clearly, additional studies are needed to discern the conditions under which H_2S functions as a vasoconstrictor, rather than its more common role as a vasodilator.

In line with its ability to relax resistance arteries, H_2S contributes to the maintenance of mean arterial blood pressure at physiological levels; pharmacological inhibition of H_2S production was shown to increase blood pressure (124, 194). Important advances in understanding the role of endogenous H_2S in vascular regulation were made in 2008 when it was reported by Yang and coworkers (183) that global deletion of CSE results in age-dependent increases in blood pressure and is accompanied by loss of endothelium-dependent dilation. On the other hand, administration of sulfide salts to anesthetized rats and mice caused a transient drop in blood pressure (23, 195). Moreover, administration of sulfide salts or the slowly releasing H_2S donor GYY4137 reduced blood pressure in a genetic model of hypertension, as well as in rats rendered hypertensive by angiotensin-II or L-NAME administration (5, 86, 196).

Vascular Permeability

Endothelial cells are responsible for the formation of a barrier between the blood and the underlying tissues (9). The stringency of barrier function even under basal conditions varies considerably between vascular beds; the two extremes are exemplified by the blood brain barrier and fenestrated and sinusoidal endothelia (4). Continuous exchange of solutes between blood and the interstitial tissue occurs in the capillaries. While basal permeability is important for tissue homeostasis, hyperpermeability is associated with several pathological/pathophysiological processes including tissue remodeling and repair, inflammation, and tumorigenesis (9, 12). In a recent study, Geng and colleagues (52) reported that H_2S inhalation decreased the permeability of the blood-brain barrier induced by cardiac arrest in rats. This effect of H_2S was attributed to reduced expression of VEGF and matrix metalloproteinase-9 (MMP-9) with enhanced expression of the permeability-reducing growth factor angiopoietin-1. An earlier study had shown that NaHS attenuated the increase in lung endothelial barrier permeability triggered by particulate matter inhalation in mice (162). In this latter study, the protective action of H_2S was mediated by reactive oxygen species (ROS) scavenging and activation of Akt. Based on the above, one would conclude that H_2S limits permeability; however, in both studies mentioned above, the biological activity of H_2S might well be indirect through antioxidant and anti-inflammatory effects attributed to H_2S (161). Moreover, H_2S is has been shown to be protective in ischemia-reperfusion injury (15, 67, 119). Therefore, H_2S protection from increased permeability during lung inflammation and following cardiac arrest might be a secondary effect, resulting from suppression of the permeability trigger.

More recently, Yuan and colleagues (187) investigated the direct effects of H_2S on vascular permeability in vitro and in vivo. Administration of diallyl trisulfide (DATS) and inorganic polysulfides increased permeability, leading to greater albumin flux and lower transendothelial resistance. Interestingly, the effect of H_2S in this study was attributed to polysulfides, rather than H_2S, as Na_2S and GYY4137 that yield low levels of polysulfides had only minor effects compared with DATS and inorganic polysulfides. The increased permeability was accompanied by disruption of endothelial junction proteins claudin 5 and VE-cadherin, along with enhanced actin stress fiber formation. Cultured endothelial cells from CSE KO mice also displayed enhanced solute barrier function while CSE KO mice were resistant to the hyperpermeability triggered by VEGF. Taken together, the available data point towards a context-dependent effect of H_2S on permeability. Clearly, additional studies are needed to dissect the direct and indirect effects on permeability that occur in physiological conditions, as well as during disease.

H_2S in Angiogenesis

In vitro studies. In healthy adult organisms, EC, although quiescent, retain their ability to form new blood vessels in pathological conditions or in response to injury (27). Upon activation, endothelial cells adopt an angiogenic program to contribute to wound healing and tissue remodeling (1). Increased angiogenesis is also observed in conditions such as psoriasis, arthritis, diabetic retinopathy, and cancer (27, 45, 46). A triad of cellular responses, namely proliferation, migration, and network formation, are crucial for EC angiogenic behavior (28). These responses are often studied in reductionist in vitro systems to predict the ability of a substance to drive angiogenesis in vivo. Several laboratories have confirmed that H_2S stimulates EC growth, motility, and organization into vessel-like structures in a variety of EC types using common in vitro assays. Studies with exogenously administered H_2S have been conducted exclusively with sulfide salts (Na_2S and NaHS) (8, 17, 26, 36, 67, 115, 121, 152). Moreover, incubation of EC with substrates for H_2S production (cysteine for CSE/CBS and 3-mercatopyruvate for 3MST) have also been shown to promote in vitro angiogenic responses (35, 36), while overexpression of CSE enhances EC growth and promotes vascular outgrowths in vitro (8, 36). In contrast, inhibition of H_2S biosynthesis with pharmacological inhibitors or silencing of CSE, CBS, or 3MST reduces cell growth, migration, and tubelike network formation (8, 35, 36, 115, 126). In line with these observations, aortic rings from CSE KO mice generated fewer tubelike structures in an in vitro angiogenesis assay (8, 36). These data suggest that both exogenous and endogenously produced H_2S are proangiogenic.

In vivo studies. The first observation of exogenous H_2S driving angiogenesis in vivo was made by Cai et al. (26), who reported that NaHS administration enhanced vascularization of

Matrigel implants. The angiogenic response to sulfide salts in vivo is eNOS dependent, as suggested by the reduced responses observed in eNOS KO mice (17, 36). Evidence that endogenous H_2S is crucial for angiogenesis in vivo came from studies in chicken chorioallantoic membranes (CAM). Treatment of CAM with the CSE inhibitors propargylglycine (PAG) and β-cyano-L-alanine attenuated vessel branching and length (115). More recently, CSE participation in VEGF-stimulated angiogenesis was confirmed in mice bearing Matrigel plug implants (73).

In line with the angiogenic role of CSE and CBS, supplementation with 3MP, the 3MST substrate, increased Matrigel plug neovascularization in mice (36). These observations taken together suggest that H_2S, irrespectively of its enzymatic source (CSE, CBS, or 3MST), promotes new blood vessel formation. This redundancy might be explained by the relatively long half-life of this gasotransmitter (142) along with its ability to freely cross membranes and diffuse into cellular compartments and microenvironments (99). Moreover, it is possible that CSE, CBS, and 3MST each have the capability to drive angiogenesis, but individual enzymes might be preferentially utilized by specific angiogenic triggers.

Mechanisms of H_2S-induced angiogenesis. To promote angiogenesis in endothelial cells, H_2S utilizes cyclic nucleotide-, kinase-, and ion channel-regulated pathways (73, 146, 161). H_2S donors stimulate Akt, p38, and ERK1/2 phosphorylation while pharmacological inhibitors of PI-3K/Akt and MAPK block EC proliferation and migration (8, 26, 67, 115). Moreover, K_{ATP} channel openers mimic H_2S responses, while K_{ATP} channel blockers reduce the angiogenic effects of H_2S (8, 26, 115, 154). In a study using human EC, K_{ATP} channels were shown to act upstream of p38 (8, 26, 115). H_2S additionally can interact with components of the NO/cGMP pathway at multiple levels (16). As expected, inhibition of eNOS, sGC, or cGMP-dependent protein kinase reduces or blunts H_2S-stimulated angiogenic responses (8, 36).

VEGF-H_2S interplay. VEGF is a prototype angiogenic growth factor, regulating new blood vessel formation in physiological, as well as pathophysiological, conditions (8, 36, 44, 59). A number of studies have established extensive cross-talk between H_2S and VEGF. Exogenously administered H_2S upregulates VEGF expression (17, 67, 79, 160), and endogenous H_2S is crucial for preserving VEGF responses; Saha and colleagues (126) demonstrated that silencing CBS in endothelial cells reduced VEGF signaling due to reduced expression of VEGF receptor 2 (VEGFR2) and neuropilin (NRP)-1. CBS-derived H_2S stabilizes specificity protein 1 (Sp1) through Cys68 and Cys755 persulfidation that is required for Sp1-mediated VEGFR2 transcription. In addition to H_2S regulation of VEGF expression, H_2S participates in VEGF signaling. We have shown that short-term exposure of human EC to VEGF increased H_2S production (115). The generated H_2S contributes to activation of downstream effectors since CSE inhibition blocked VEGF-stimulated p38 and ERK1/2 activation (115). Thus, VEGF-stimulated angiogenesis in endothelial cells is attenuated by pharmacological inhibition or silencing of CSE/CBS (36, 115, 121, 126). Finally, H_2S was shown to potentiate the activation of VEGFR2 after VEGF binding (152). Tao and colleagues (152) identified the existence of a disulfide bond between Cys1045 and Cys1024 of VEGFR2 that is inhibitory for the tyrosine kinase activity of the receptor. Nucleophilic attack of the disulfide bond by H_2S leads to a disulfide reduction and boosts VEGFR2 tyrosine kinase activity.

Angiogenesis in the context of injury or disease. After establishing a role for H_2S in angiogenic responses in physiological conditions, the role of H_2S as a proangiogenic substance was investigated in conditions such as tissue ischemia, heart failure, wound healing, and cancer (36, 78, 115, 118, 145). Two independent studies using sulfide salts (17, 160) and one using diallyl trisulfide (78) have shown H_2S to increase angiogenesis and restore ischemic tissue function. The H_2S donors have beneficial effects in hindlimb ischemia by enhanced NO production via eNOS-dependent and independent mechanisms and increased hypoxia-inducible factor-1α (HIF1α) expression and activity (17). In the same model, as well as in a model of myocardial ischemia, the H_2S precursor *S*-propargyl-cysteine promoted angiogenesis and improved tissue perfusion (72). In rats with cerebral artery occlusion, treatment with a sulfide salt increased endothelial proliferation and angiogenesis in the peri-infarct area, improving the functional outcome (67). In a femoral artery ligation study, arteriogenesis was inhibited in the absence of CSE, with a significant reduction in mature vessel density, angiogenic indices, and blood flow in CSE KO mice compared with WT mice (78). Similarly, $CBS^{+/-}$ mice exhibited reduced arteriogenesis/angiogenesis that was due to impaired Akt phosphorylation associated with hyperhomocysteinemia (18).

The slow-releasing H_2S donor GYY4137 was used to evaluate post-ischemia cardiac remodeling. GYY4137-treated animals exhibited reduced left ventricular (LV) size and preserved function (90). These beneficial effects coincided with greater vessel density in the LV area. Similarly, diallyl trisulfide (DATS), a naturally occurring H_2S donor, improved LV remodeling and preserved LV function after aortic constriction (118). H_2S donor administration shifted the angiogenic balance by increasing VEGF and reducing angiostatin expression. DATS treatment led to increased Ki67-stained EC and increased cardiac vascular density.

Increased angiogenesis is one of the hallmarks of cancer. A number of reports have indicated increased expression of H_2S producing enzymes in cancer (142). The importance of elevated concentrations of H_2S in tumor angiogenesis was highlighted in studies from three laboratories. Inhibition of CSE decreased vascularization of clear cell renal cell carcinoma (ccRCC) xenografts grown on CAMs (137). Moreover, the CBS/CSE inhibitor AOAA reduced CB31-positive vessel structures in colon cancer xenografts (145) and ovarian cancer cells with silenced CBS induced less angiogenesis in the tumor (14). It is likely that intratumor angiogenesis is stimulated both by tumor-derived as well as host-derived H_2S production, although the relative contribution of the various potential sources remains to be further explored.

Antioxidant and Anti-Inflammatory Effects of H_2S in the Vessel Wall

Enhanced oxidative stress is a key event for diseases affecting the vessel wall including hypertension, atherosclerosis, and vascular diabetic complications (84, 96, 135). H_2S inhibits ROS production, but also eliminates ROS by direct scavenging, upregulation of GSH, and increased expression of antioxidant enzymes (112, 120, 144, 174). H_2S would thus be

expected to counteract many of the oxidative stress-related changes in the vessel wall. Indeed, administration of NaHS to mice rendered hypertensive by angiotensin II infusion reduced aortic NADPH-dependent superoxide generation and improved ACh-induced relaxation (5). Similarly, H_2S reduced the levels of ROS in endothelial cells cultured in high glucose, preventing apoptosis and endothelial cell injury (53, 57). Adenovirus-mediated gene transfer of CSE or administration of a sulfide salt in hyperglycemic conditions reduced ROS production and improved endothelial-dependent vascular relaxation, while CSE knockdown led to a greater impairment in endothelial function (141). Moreover, pretreatment with NaHS reduced the intracellular reactive oxygen species levels, suppressed NF-κB activity, and inhibited the expression of intercellular adhesion molecule-1 (ICAM-1) in cells cultured in high glucose (56).

Antioxidant effects of H_2S have also been demonstrated in the context of atherosclerosis, leading to delayed progression and/or restricting the severity of the disease. H_2S administration was shown to inhibit lipid hydroperoxide formation in LDL and to protect against oxLDL cytotoxicity (68, 105). Moreover, H_2S inhibited oxLDL-induced intracellular lipid accumulation and foam cell formation (173, 198). The mechanism through which H_2S reduced OxLDL-uptake was K_{ATP} dependent and involved reduced expression of CD36, scavenger receptor A, and acyl-coenzyme A:cholesterol acyltransferase-1 (198). On the other hand, reducing H_2S production through pharmacological inhibition of CSE led to enhanced oxLDL binding and uptake in macrophages, potentiating the accumulation of total and esterified cholesterol (198). Thus, maintaining H_2S levels is important to offset the initial events of atheroma formation. The existence of an inverse relationship between H_2S and oxLDL was reinforced by the observation that oxLDL upregulates DNA methyltransferase expression and activity, leading to hypermethylation of CpG rich regions in the CSE promoter and reduced CSE transcription (42).

Monocyte recruitment and accumulation is a key event in vascular inflammation and atherosclerosis and depends on the expression of the cellular adhesion molecules ICAM-1, VCAM-1, and P-selectin (123). ICAM-1 levels were reduced in aortas of ApoE KO mice following treatment with a sulfide salt (166). The mechanism of H_2S-induced inhibition of ICAM-1 expression was addressed in cultured endothelial cells, where it was shown that NaHS limits the degradation of IκB-α, inhibiting NF-κB activation. The impact of NF-κB activation on adhesion molecule expression was also investigated in a study by Pan and colleagues (114), who observed that exogenous H_2S blocked the adhesion of U937 cells to TNF-α-activated HUVECs. In the same study, NaHS also abrogated intracellular ROS triggered by TNF-α treatment (114). In agreement to the reduction in adhesion molecule expression observed after treatment with exogenous H_2S, inhibition of CSE upregulated leukocyte function-associated antigen-1 and ICAM-1 on the cell surface and enhanced leukocyte adherence to the vessel wall (189). The anti-inflammatory effects of H_2S on leukocytes are not restricted to interference with homing and transmigration, but extend to the production of proinflammatory mediators. H_2S has been shown to reduce inflammatory cytokine levels, including IL-1β, TNF-α, and IL-6 from monocytes/macrophages; similar inhibitory effects on cytokine production have been noted in endothelial cells (98, 161).

Regulation of smooth muscle phenotype (synthetic vs. contractile) by environmental cues plays an important role in vascular pathologies (113). It has been proposed that H_2S coordinates the expression of proliferative and contractile proteins favoring a differentiated smooth muscle cell phenotype (181). Smooth muscle cells from CSE KO animals display increased proliferation in vitro and in vivo, while H_2S donors or CSE overexpression inhibits vascular smooth muscle cell growth and promotes apoptosis in cultured smooth muscle cells (43, 180, 182, 184). H_2S also reduces smooth muscle migration (178). These observations are in line with findings that reduced H_2S production leads to increased neointimal formation (101, 178). Thus, the above-mentioned effects of H_2S on smooth muscle cell behavior contribute to its antiatherosclerotic effects and its ability to inhibit aberrant vascular remodeling in response to injury (98).

Alterations in H_2S Levels and Signaling in the Vasculature During Disease

Cardiovascular disease is a contributing factor to the morbidity of many diseases, and damage to the vasculature mediates much of this pathology. It is now becoming clear that loss of H_2S production contributes to at least some of the vascular dysfunction in cardiovascular disease (7, 21, 37, 94, 163). Dysregulation of H_2S-related pathways has been reported in hypertension. CSE levels are reduced in the vessel wall of spontaneously hypertensive rats, and both CSE and CBS are reduced in the resistance vessels of rats rendered hypertensive after dexamethasone treatment (24, 39, 177). In addition, animals with salt-sensitive hypertension have lower levels of CBS (62). A causal link between low CSE levels and high blood pressure was established following the observation that CSE KO mice exhibit hypertension. Reduced H_2S plasma levels have been confirmed in a human cohort of hypertensive patients (81, 139). In several studies, administration of H_2S donors to hypertensive animals lowers mean arterial blood pressure and reverses vascular remodeling associated with hypertension (reviewed in refs. 100, 157).

Atherosclerosis is a disease with strong indications that loss of H_2S contributes to the establishment and progression of the disease. Feeding CSE KO mice a high-fat diet leads to increased fatty streak formation, enhanced oxidative stress and expression of adhesion molecules and intimal proliferation (97). Atherosclerosis development in this model was reversed by exogenous H_2S administration. In ApoE KO animals, inhibition of CSE increased the chemokine/chemokine receptor CX3CR1 and CX3CL1 and exacerbated atherosclerosis (190). Moreover, double CSE/ApoE KO animals displayed more extensive atherosclerotic lesions than ApoE KO mice; the double KO phenotype could be rescued by exogenous administration of NaHS. Administration of NaHS to high-fat-fed (HFD) ApoE KO mice not only reduces vascular O_2^- generation and lesion area, but also improves early signs of endothelial dysfunction as it improves endothelium-dependent vascular relaxations (47). However, H_2S might have differential effects in developing versus established atherosclerosis. Intraplaque angiogenesis predisposes to plaque vulnerability (102) and H_2S is a proven angiogenic stimulus. In a recent study, van den Born et al. (156) found high CSE expression in human atherosclerotic plaque microvessels. Thus, although CSE/H_2S

prevent lesion formation, it is likely that in established atheromas it could trigger plaque rupture.

Intervention studies in isolated cells and animal models of atherosclerosis offer potential mechanisms for this apparent protective effect of H_2S. Dosing HFD ApoE KO mice with H_2S-releasing aspirin, *S*-aspirin, decreased both chemokine receptor levels and aortic lesion size compared with mice receiving normal aspirin (191). Transgenic overexpression of CSE in ApoE KO mice ameliorated the lipid profile, downregulated NF-κB activation, and reduced lesion formation (33), further suggesting that the CSE/H_2S pathway is a promising therapeutic target against atherosclerosis. In a study by Liu and colleagues (93), administration of an H_2S donor GYY4137 to ApoE KO mice similarly decreased plaque size as well as the formation of proinflammatory cytokines and superoxide levels. A more recent study from this same group reported that treatment with an H_2S donor reduces plaque formation by increasing translocation of the antioxidant transcription factor Nrf-2 with a resultant increase in hemeoxygenase-1 synthesis (173). The mechanism of H_2S activation of Nrf-2 required sulfhydration of Cys151 in the Nrf-2 suppressor Keap-1, leading to dissociation of Keap-1 from Nrf-2 and subsequent activation of downstream antioxidant pathways. This pathway has also been implicated in the antiaging effects of H_2S in embryonic fibroblasts from wild-type (WT) and CSE knockout mice (185). Alternatively, treatment with an H_2S donor might also protect the vascular wall by increasing generation of NO. A 2016 study in ApoE KO mice on a western diet observed a reduction in plaque formation in mice treated with the H_2S donor NaHS that was accompanied by increased plasma levels of NO_x and increased protein nitrosylation. Furthermore, inhibition of CSE with propargylglycine (PAG) decreased plasma NO_x and augmented lesion formation (91). Thus, H_2S appears to activate antioxidant pathways in the vascular wall to preserve or increase the activity of NO and to decrease the generation and activity of proinflammatory cytokines.

In chronic hemodialysis patients, those with accelerated atherosclerosis had lower plasma levels of H_2S than the healthier hemodialysis patients with less vascular disease (163), and in dialysis patients with diabetic nephropathy, the plasma level of H_2S was negatively correlated with both the degree of atherosclerosis and the levels of the inflammatory marker MMP-12 (83). In healthy subjects, plasma H_2S correlated positively with levels of the protective factors of adiponectin and HDL, but negatively with the atherosclerotic risk marker, LDL (65). This relationship of lower H_2S levels in the most severely affected individuals is also reported in patients with coronary artery disease along with a negative correlation of H_2S and chemokine receptors on circulating monocytes (50).

Similar to studies in atherosclerosis, diabetes in humans with or without the comorbidity of elevated lipids is generally associated with decreased plasma levels of H_2S (64–66, 155). In addition, animal models of diabetes have also been reported to have decreased plasma or tissue levels of H_2S (20, 32, 64, 69, 138, 141, 144, 159). However, there are several anomalous reports of elevated H_2S synthesis in diabetes. For example, streptozotocin-induced diabetes in rats was associated with elevated levels of H_2S in both the liver and the pancreas (188). This 2005 study reported that insulin therapy decreased expression of CBS and CSE, restoring enzyme expression and H_2S to control levels and demonstrating that insulin may be an endogenous regulator of H_2S production. In diabetic Zucker rats, increased production of H_2S in pancreatic cells was associated with suppressed insulin levels (171). Suppression of H_2S production with PAG increased circulating insulin and reduced hemoglobin A1c levels, leading the authors to conclude that excess pancreatic production of H_2S in this model of type 1 diabetes suppresses insulin secretion leading to impaired glucose homeostasis. Thus excessive H_2S production with subsequent activation of K_{ATP} channels in pancreatic islet cells might be one mechanism of insulin dysregulation. However, in human and animal studies of type 2 diabetes, it is increasingly apparent that obesity is associated with decreased production of H_2S and this decreased production appears to contribute to diabetic nephropathy (3, 13, 125, 175). Thus future studies examining the sites and mechanisms of H_2S regulation of renal function are needed to interrogate this system for potential new therapies to preserve renal function in diabetes.

Defective H_2S production has also been shown to occur in other vascular pathologies. In a recent study, Gomez et al. (55) reported reduced CSE expression and H_2S levels in abdominal aortic aneurisms in a small human cohort, extending observations made in animal models (181). Moreover, the CSE/H_2S pathway has been shown to be downregulated in an animal model of vascular calcification in a NaHS-reversible manner (172, 186). The protective effect of H_2S was reported to be dependent on endoplasmic reticulum (ER) stress inhibition (186). These observations are in agreement with the use of sodium thiosulfate, an agent that generates H_2S (136), as a treatment for calciphylaxis in humans.

Conclusions and Future Directions

In conclusion, H_2S, a ubiquitous gasotransmitter signaling molecule, exerts a multitude of beneficial effects in the vessel wall including suppression of oxidative stress, inhibition of inflammation, and enhancement of vasodilation. Suppression of H_2S levels (either by increased H_2S consumption and/or decreased H_2S production) exacerbates a variety of cardiovascular diseases including atherosclerosis and diabetic vascular complications. Under such conditions, therapeutic replacement of H_2S may be a future therapeutic option. The role of H_2S in the context of angiogenesis, in some cases, is beneficial: in the context of post-ischemic revascularization, it promotes physiological angiogenesis so that stimulation of these responses by H_2S donors may be of future therapeutic benefit. However, in other cases, pathological neovascularization may involve increased H_2S production such as during the development of retinopathy (54) or in the context of cancer angiogenesis (142); in such cases, inhibition of H_2S production may be a potential future therapeutic approach. Intensive efforts are under way to identify and optimize both donors of H_2S (169, 170, 176, 197) and inhibitors of H_2S biosynthesis (10, 19, 30, 41, 149); after successful preclinical to clinical translation, such compounds may enhance the therapeutic arsenal against multiple cardiovascular diseases. It is also worth emphasizing that the cardiovascular effects of H_2S often require the functional integrity of the eNOS/cGMP pathway; when NO is not produced, many of the angiogenic and some of the vasodilatory effects of H_2S are lost (reviewed in ref. 143); this interdependence of the two pathways should also be considered when designing H_2S (or NO)-based therapeutic approaches in the future. Finally, the

signaling pathways regulating acute activation of H_2S-synthesizing enzymes is not well understood and defining upstream regulators of CSE, CBS, and 3MST will potentially allow the development of additional therapeutic agents to manipulate this pathway.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

N.L.K., C.S., and A.P. drafted the manuscript; N.L.K., C.S., and A.P. edited and revised the manuscript; N.L.K., C.S., and A.P. approved final version of the manuscript.

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