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H_2S in the Vasculature: Controversy of Mechanisms in Physiology, Pathology and Beyond

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Abstract

Hydrogen sulfide (H_2S) is an endogenously gaseous messenger with a number of physiological effects. Pharmacological and genetic models point toward an important role for this vasodilator gas in the regulation of vascular tone, cardiac response to ischemia/reperfusion injury, and inflammation among others. Understanding the complex interaction of H_2S with basic cellular signaling and its impact on endothelial and smooth muscle physiology may provide insights into the early stages of developing vascular inflammation and atherosclerosis or related vascular pathologies. The underlying mechanism of action is not completely understood. Recent evidence suggests a key role of H_2S in protecting mitochondria against oxidative damage, regulation of ion channels and modulation of eNOS activity. This review will focus on the key role of H_2S in the regulation of vascular function including free radical production and its physiological role in health and disease.

Keywords: Hydrogen sulfide; Gasotransmitter; Atherosclerosis; Oxyhemoglobin; EDHF

Abbreviations: ↑: increase/activate; ↓: decease/inactivate/inhibit; AA: arachidonic acid; cAMP: Cyclic Adenosine Monophosphate; ADRF: Adipocyte-Derived Relaxing Factor; BK_{Ca}: Large Conductance Ca2+-activated K+ channels; cGMP: Cyclic Guanosine Monophosphate; CSE: Cystathionine γ-lyase; ECs: Endothelial Cells; EDHF: Endothelium-Derived Hyperpolarizing Factor; eNOS: Endothelial Nitric Oxide Synthase; HEK: Human Embryonic Kidney; HUVECs: Human Umbilical Vein Endothelial Cells; IK_{Ca}/SK_{Ca}: Intermediate and Small Conductance Ca^{2+}-activated K+ channels; K_{ATP}: ATP Sensitive K+ channels; K_{Ca}: Ca^{2+}-activated K+ channels; K_V: Voltage- gated K+ Channels; NO: Nitric Oxide; NOX-1: NADPH oxidase 1; O^- : superoxide; PDE: Phosphodiesterase; PLA2: Phospholipase A2; VSMCs: Vascular Smooth Muscle Cells

Introduction

Hydrogen sulfide (H_2S) is colorless, water soluble, flammable gas with a strong smell that dissociates into H^+, HS^-, and S^{2-}, H_2S is an endogenous signaling molecule also known as a gasotransmitter. Recent studies have indicated that H_2S has several important effects on cardioprotection, hepatoprotection, ion channels, protein modifications, mitochondrial metabolism, oxidative stress, and anti-apoptotic nature [1]. H_2S is produced endogenously by both enzymatic and non-enzymatic pathways [2]. In mammalian tissues, H_2S is mostly synthesized from L-cysteine by three enzymes:

Cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST) [3]. In the vasculature, H_2S is produced in both the vascular endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) by CSE [2,4-7]. CSE is a pyridoxal 5'-phosphate-dependent cytosolic enzyme and CSE activity is regulated by intracellular Ca^{2+} concentrations [8]. H_2S is synthesized by CSE in several different reactions:

1. Cysteine + H_2O → pyruvate + $\mathbf{H_2S}$ + NH_3,

2. homocysteine → α-ketobutyrate + $\mathbf{H_2S}$ + NH_3,

3. homocysteine + homocysteine → homolanthionone + $\mathbf{H_2S}$,

4. Cysteine + homocysteine → cystathionine + $\mathbf{H_2S}$ [9,10].

3-MST, along with cysteine aminotransferase (CAT) or D-amino acid oxidase (DAO), produces H_2S from cysteine and α-ketoglutarate in the mitochondria [11,12]. 3- MST/CAT is localized in thoracic aorta ECs and produces H_2S [13]; however, a vascular effect of 3-MST/CAT-derived H_2S is unknown. Endogenous intra mitochondrial 3-MST-derived H_2S has been shown to protect mitochondrial function/metabolism [14].

Compared to the understanding of H_2S biosynthesis, H_2S metabolism is poorly understood. H_2S is enzymatically metabolized by H_2S oxidation pathways in mitochondria:

1. H_2S → oxidized by sulfide quinone oxidoreductase → persulfide,

2. Persulfide → further oxidized by sulfur dioxygenase → sulfite (H_2SO_3),

3. H_2SO_3 → metabolized by rhodanese → thiosulfate ($H_2S_2O_3$) → excretion (kidneys) [15].

Other known pathways of H_2S metabolism are:

- Methylation by S-methyltransferase to methanethiol and dimethylsulfide in cytosol [16]

- Scavenged by oxyhemoglobin, methomoglobin, and metallo- or disulfide-containing molecules [2,16-18].

While the physiological effects of H_2S in the vasculature have been studied for almost two decades, and its vasoactive properties and effects on cellular proliferation and vascular remodeling are known,

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the intracellular signaling pathways of H_2S are not yet determined. Similarly there is a disagreement as to whether H_2S contributes to the development of atherosclerosis, is vasoprotective, or possibly both. This review paper summarizes the effects of H_2S in the vascular system under physiological and pathological conditions. It also highlights the possible mechanisms involved with how H_2S signaling may contribute to the development of cardiovascular diseases. Figure 1 summarizes and gives an overview of the complex signaling events related to H_2S in the vasculature endothelium and smooth muscle cells.

H_2S in the Vasculature

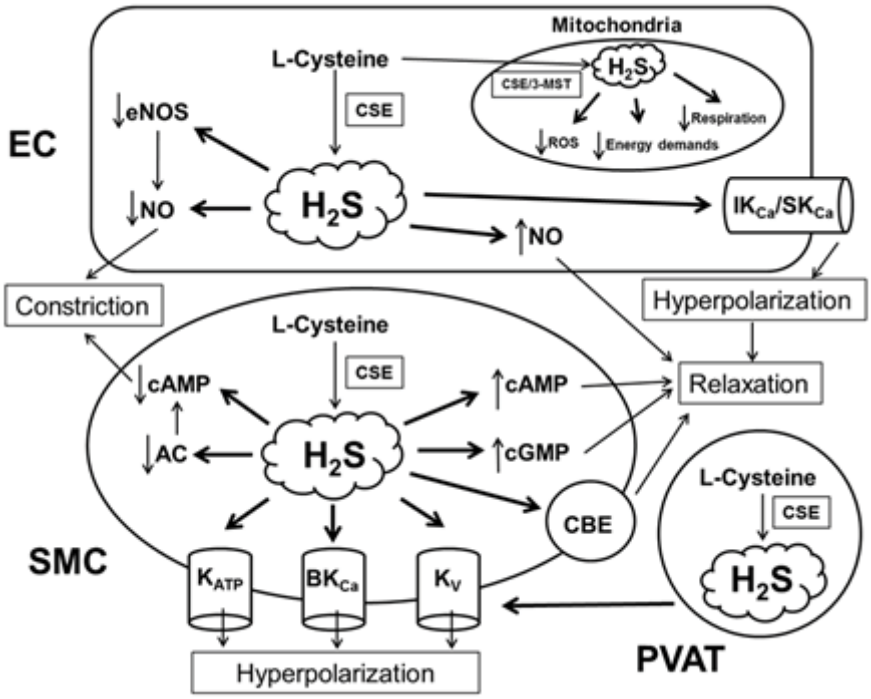
The following section summarizes the numerous effects of H_2S on the vasculature and highlights some of the contributing factors.

H_2S induces both vasoconstriction and vasorelaxation. An increasing number of reports show that contribution of H_2S depends on vascular beds tested (e.g., aorta *vs*. mesenteric artery), vessel size (conduit *vs*. resistant) [5], endothelium (intact vs. denuded), gender [19], duration, concentration, and rate of administration of H_2S or its donor (e.g., NaHS). Other factors influencing H_2S response in the vasculature are model organisms and the preconstriction methods (e.g., phenylephrine, U46619) [20,21]. It is established that H_2S induces a biphasic vascular response as lower doses tend to be vasoconstrictors, while higher doses are generally speaking vasodilators. For example, the H_2S donor NaHS at a lower concentration (< 100 μM) induces vasoconstriction but at a higher concentration (>100 μM), is a vasodilator in isolated rat mesenteric arteries [21]. Table 1 gives a summary of the established vasoactive mechanisms of H_2S in human, swine, rodent, and cultured cells.

The mechanism of H_2S-induced vasoconstriction seems to mainly be inactivation of NO [22,23], inhibition of endothelial nitric oxide synthase (eNOS) activity/NO production [24-26], and down regulation of cAMP [27]. Mechanisms of H_2S-induced vasodilation consist of several complex pathways, including regulation of various ion channels, reduction of intracellular pH in SMCs [28], increase in cAMP production [29], and increase in cGMP by inhibition of phosphodiesterase (PDE) [30]. Furthermore, H_2S has been shown to act as an adipocyte-derived relaxing factor (ADRF) [10], and as an endothelium-derived hyperpolarizing factor (EDHF) [19]. Although the mechanisms of H_2S-induced vasodilation need to be explored further, its known functions suggest a significant role in a number of mechanism that contribute to the development of cardiovascular disease (CVD) therefore making it an attractive clinical target. To further the understanding of how H_2S contributes to the development of cardiovascular disease, it will be of critical importance to determine the effective doses in physiological and pathological circumstances.

Cellular Proliferation, Vascular Remodeling and Atherosclerosis

Since H_2S has similar physiological effects as NO increasing cardiovascular protective effects have been published. While both NO and H_2S have been shown to be vasodilators their mechanisms of action differ significantly. Unlike NO, which signals via the cGMP pathway,



H_2S is synthesized by CSE in both ECs and SMCs. H_2S may cause vasoconstriction by inhibiting eNOS activity, NO production, and down regulating cAMP. H_2S may activate IK_{Ca}/SK_{Ca}, BK_{Ca}, K_{ATP}, K_V, and CBE channels and increase cAMP, cGMP, and NO levels to induced vasorelaxation. PVAT-derived H_2S also activates K_V (KCNQ) channels. H_2S reduces mitochondrial energy demands, ROS production, and respiration to reserve mitochondrial function.

3-MST=3-mercaptopyruvate sulfurtransferase; AC=adenylate cyclase; BK_{Ca}, large conductance Ca^{2+}-activated K^+ channels; cAMP=cyclic adenosine monophosphate; CBE=Cl^-/HCO_3^- exchanger; cGMP=cyclic guanosine monophosphate; CSE=cystathionine γ-lyase; EC=endothelial cell; eNOS=endothelial nitric oxide synthase; IKCa/SKCa=intermediate and small conductance Ca^{2+}-activated K^+ channels; K_{ATP}=ATP-sensitive K^+ channels; K_V=voltage-gated K^+ channels; NO=nitric oxide; PVAT=perivascular adipose tissue; SMC=vascular smooth muscle cell.

Figure 1: Signaling pathways for H_2S-induced vasoconstriction and vasodilation.

Species	Vascular bed	Mechanism	Physiological effect	Reference
Human	Internal mammary artery	Vasoconstriction: ↓NO Vasodilation: ↑Opening of K_{ATP}	Biphasic vasoactive effect (constriction at lower dose, relaxation at higher dose)	[63]
	VSMCs	↑cAMP level by ↓O_2 formation through NOX-1 expression and Rac1 activity	Vasorelaxation	[29]
	HUVECs	↑eNOS	Vasorelaxation	[59]
	HEK-293 cells	Opening K_{ATP} by S-sulfhydration at extracellular cysteine residues (C6 and C26) of SUR1 subunit	Membrane hyperpolarization	[64]
Bovine	Arterial ECs	↑Enos, ↑NO	Vasorelaxation	[60]
Swine	Cerebral artery	↑Opening of BK_{Ca}	Vasorelaxation	[65]
Rat	Aorta	Vasoconstriction:↓eNOS Vasodilation: ↑Opening of K_{ATP} EC- dependent	Biphasic vasoactive effect (constriction at lower dose, relaxation at higher dose)	[23,24]
		Vasoconstriction: ↓NO by HCO_3^-	Biphasic vasoactive effect (constriction at lower dose, relaxation at higher dose)	[26]
		↓cAMP level	Vasoconstriction at low dose	[27]
		↑cGMP level by ↓PDE	Vasorelaxation	[30]
	Aorta and mesenteric artery	EC_{50} of H_2S, 125 ± 14 μM in aorta vs. 25 ± 3 μM in mesenteric artery	Vasorelaxation: Resistance vessels > Conduit vessels	[5]
		↑Opening of K_{ATP}	Vasorelaxation/hyperpolarization	[5,7,66]
	Coronary artery	↑Opening of K_V	Vasorelaxation	[67]
	In vitro (aorta) and *in vivo*	↓NO production, eNOS activity, L- Arginine uptake and transport	Downregulate L- Arginine/eNOS/NO pathway	[25]
	Mesenteric artery	Vasoconstriction: ↑AA release by ↑PLA2 Vasodilation: by cytochrome P450- derived metabolites	Biphasic vasoactive effect (constriction at lower dose, relaxation at higher dose)	[20]
		↑Opening of IK_{Ca}/SK_{Ca}	Vasorelaxation	[5,20]
	Mesenteric artery/VSMCs	↑Opening of BK_{Ca}, EC-dependent	Vasorelaxation	[68,69]
	VSMCs (aorta)	↑CSE expression by NO	Vasorelaxation	[7]
		↓intracellular pH via ↑Cl-/HCO_3^- exchanger	Vasorelaxation	[28]
Mouse	Aorta	Vasoconstriction: ↓eNOS	Biphasic vasoactive effect (constriction at lower dose, relaxation at higher dose)	[24]
	Coronary artery	↑Opening of BK_{Ca} and K_V ↓Sheer stress medicated dilation	Vasorelaxation	[61]
	Mesenteric artery	↑Opening of K_{ATP}	Vasorelaxation	[70]
		↑Opening of IK_{Ca}/SK_{Ca} EDHF	Vasorelaxation	[19,70]
	Mesenteric artery/SMCs	↑Opening of K_V (KCNQ) by perivascular adipose tissue derived-H_2S (as an ADRF)	Vasorelaxation	[10,71]
	VSMCs (aorta)	Hyperpolarization in females but not males	Gender difference in membrane hyperpolarization	[19]

Table 1: Physiological Effects of H_2S in Different Vascular Beds and Species.

H_2S is believed to activate a host of different ion channels directly. Researchers are not clear how the vessel-relaxing responsibilities are shared between NO and H_2S. Some evidence suggests that NO contributes mainly to conduit vessel-relaxation, while H_2S appears to work mainly in smaller blood vessels [31]. While the signaling properties under physiological conditions are being slowly uncovered, actions under pathological conditions are less defined. H_2S has previously been described to contribute to angiogenesis [32], collateral growth [33], and vascular proliferation [34]. Under pathological conditions, these same signaling events can lead to the development of atherosclerosis, a key factor in the development of CVD. Unregulated cellular proliferation and other shared signaling cascades contribute to the inward remodeling of the vasculature, one of the hallmarks of atherosclerosis. The exact mechanism of how H_2S contributes to this process remains elusive. While the major source of H_2S in plasma is likely produced by VSMCs [35], ECs have been recognized to contribute to the vascular effects stimulated by H_2S [36]. This divergence could contribute to the biphasic phenotypes observed with H_2S in vascular signaling (proliferative/antigenic nature vs. atheroprotective nature).

One of the major contributors to the development of vascular abnormalities is defects in mitochondrial oxidative phosphorylation and mitochondrial reactive oxygen species (ROS) production. In fact, the major EDHF in response to flow stimulus in subjects with coronary artery disease (CAD) is mitochondria-derived H_2O_2 [37], [38]. Mitochondria are the major energy factories of most cells, where ATP is produced via oxidative phosphorylation. Increased production of ROS in mitochondria (mt), alongside accumulation of mtDNA damage and progressive defects in respiratory chain function, are fundamentally linked to a broad number of cardiovascular diseases (CVD). Recently, H_2S has emerged as a key regulator of mitochondrial energy production. For example, a significant reduction of energy demand by H_2S has been established [39], and like nitric oxide, H_2S results in mitochondrial protection and reduced ROS production [40].

In isolated mouse cardiac mitochondria, the H_2S donor Na_2S improves posthypoxic mitochondrial respiration rate and restores mitochondrial function after 30 min of hypoxia [41]. Furthermore, H_2S has been show to suppress H_2O_2 induced cellular senescence [42]. As mitochondrial ROS has quickly become one of the phenotypic

hallmarks of cardiovascular diseases, the exact regulatory system is not well defined. We have learned from several genetic disorders (e.g., Ataxia-Telangiectasia, Down Syndrome, Fanconi Anemia and Werner Syndrome) that mitochondrial dysfunction is a significant contributor to the development of cardiovascular phenotypes in these genetic diseases (reviewed by [43]). Similar to H_2S, the catalytic subunit of telomerase (TERT), a nuclear enzyme crucial for telomere maintenance, has been shown to have mitochondrial protective properties. Telomerase is an established regulator of cellular senescence and tissue aging. TERT has been shown to co-localize with the mitochondria where it also suppresses mtROS formation under stress conditions [44-46]. TERT, like H_2S, is increased in VSMC proliferation but also shows protective effects in other cells types, including the endothelium [46-49]. As increasing evidence show overlapping cellular phenotypes and interaction with similar signaling pathways (e.g., tyrosine kinase signaling [50,51], MAP kinases [52,53]), more detailed investigation of their connection is warranted in order to define these complex interactions.

Physiology vs. Pathophysiology

As part of the gas transmitter family of signaling molecules, the field of H_2S physiology has grown rapidly over the last decade. Interactions of H_2S and other gasotransmitters, sulfurating modification of proteins and the functional role of H_2S in multiple systems has shed light on its important role in the vasculature. Both preclinical and human studies have shown that disturbed synthesis of H_2S could contribute to pathologies of cardiovascular diseases. The definitions of physiological and super physiological, aka pathological, levels of H_2S are controversial. Physiological levels of H_2S in the vasculature seem to vary with methods of measurements, tissues, and species. Whiteman and Moore summarized that endogenous level of H_2S in plasma or serum is between 23-60 μM in rodents and adult humans [54]. Polmemus and Lefer concluded that blood concentration of H_2S is high nM to low μM and half-life (*in vivo*) is seconds to minutes [55]. Novel methods to measure steady-state and fluctuating levels of H_2S are needed to define a clear range of protective/positive effects on the vasculature and other organs.

While H_2S acts as a physiologically significant vasodilator, vasoconstrictor properties have also been identified and described. For example, H_2S has clear inhibitory effects on eNOS and produces a contractile response in the mouse aorta. H_2S also causes impairment of acetylcholine-mediated dilation likely via its direct inhibitory effect on eNOS [56]. Similarly, Zhao and colleagues showed that H_2S-induced vasorelaxation is attenuated by removal of the endothelium as well as NOS inhibition by L-NAME [57]. Furthermore, H_2S pretreatment blunted the effect of the NO donor, sodium nitroprusside. A more detailed overview of the overall effects of H_2S in health and disease is reviewed elsewhere [58].

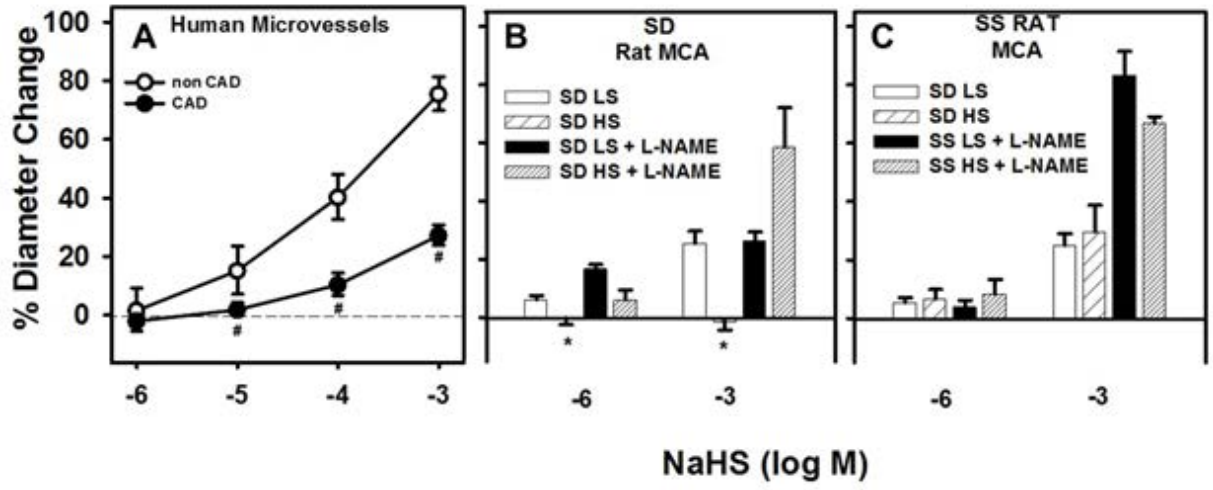
While the role of H_2S in the pathogenesis of hypertension and vascular abnormalities is well documented [54,55], including regulation of the renin angiotensin system [24], the opposite question of how the physiological effects of H_2S are regulated under pathological conditions is less known. Increasing evidence is demonstrating that inhibitors of H_2S production or external H_2S donors have significant effects in various animal models of inflammation, reperfusion injury and circulatory shock [21]. The effects in human vessels or basic disease models and its underlying signaling properties, however, lag behind. Figure 2a shows that in isolated microvessels from subjects with coronary artery disease, the vasodilator response to H_2S is markedly reduced, underlining a need for further study in human tissue and subjects. As studies in human vasculature are significantly more involved and restricted than animal studies future investigations of mechanism should go hand in hand. We need to use findings in the human vasculature to guide mechanistic studies in rodent and other preclinical studies. Using the well-established rat model of salt sensitive hypertension, we have observed a significant difference in the magnitude of H_2S -induced dilation compared to normal controls as illustrated in Figure 2b. H_2S -induced vasodilation in cerebral vessels from normal Sprague Dawley (SD) rats was eliminated by a high salt (HS) diet (3 days 4% NaCl). High salt diet is known to lower circulating angiotensin II (ANG II) signaling and with that significantly contributes to vascular, renal and other forms of hypertension. To our surprise in Dahl salt sensitive (SS) rats, a known model of chronically low plasma renin activity and low levels of circulating ANG II, vasodilation to H_2S was preserved even after treatment with HS diet. These findings suggest that an acute increase in salt load can block H_2S induced vasodilation by reducing the activity of the renin angiotensin system under physiological conditions. One potential mechanism of action could be the well-established effects of cAMP on renin expression [22] and signaling by the vascular renin-angiotensin system, as H_2S is also known to be a regulator of cAMP homeostasis [22]. In the SS models of salt sensitive low renin (and low ANG II) hypertension, H_2S -mediated vasodilation is preserved, suggesting an alternative pathway mediating the effects of H_2S in the vasculature as the effects of lowered cAMP no longer have physiological consequences via the renin angiotensin system.

While it is known that H_2S signaling overlaps with NO signaling, the details of these interactions are still being investigated. For example, NO donors upregulate the expression of CSE in cultured rat aortic SMCs in a concentration-dependent manner, suggesting NO increases the production of H_2S [7]. In line with these findings, our data presented in Figure 2c shows that inhibition of NOS with L-NAME in SS rats and healthy SD rats increases sensitivity to H_2S (one would expect this with a decrease in CSE expression due to decreased NO levels). The effects of H_2S on NO are somewhat controversial. NaHS or Na_2S increases NO production/eNOS phosphorylation at Ser-1177 in cultured endothelial cells [59,60], while, NaHS or Na_2S inhibits eNOS activity *in vivo* [61,62] and *in vitro* [25]. Additional studies are necessary to completely untangle this complicated signaling network.

Together these concepts suggest that different signaling events govern the effect of H_2S on the vasculature under so-called physiological conditions and acute stress responses *vs.* prolonged systemic exposure to external stressors (in this case salt load). Whether H_2S as a vasodilator is critical during acute changes of vascular environment (e.g., circulating factors, ROS, EDHF production) or as an activation of endogenous defense systems under chronic conditions remains to be determined.

Short Summary and Concluding Remarks

The recent progress made to understand the contribution of H_2S in the vasculature has been significant. Increasing evidence suggests physiological roles of this gasotransmitter in control of vascular reactivity with both contractile and dilator properties. The role of H_2S in pathophysiological hypertension, heart disease and inflammation is now well-accepted. Development of H_2S drugs is progressing and some clinical studies have been published (clinicaltrials.gov). Genetic models (e.g., CSE knockout mouse) have been generated and should contribute to the understanding of the physiological implication of this novel signaling molecule. However, despite this significant increase in our understanding of H_2S and its role in the vasculature, its relevance on the organism level (e.g., blood pressure control) is still



Human microvessels or rat middle cerebral vessels (MCA) were isolated from fresh tissue and cannulated onto glass pipettes of equal impedance as published previously [72,73]. After preconstriction (human= ET-1; rat= myogenic tone), dilation to increasing amounts of the H_2S donor NaHS were performed. A). In human microvessels from individuals with no clinical diagnoses of coronary artery disease (CAD), a solid dilation to increasing doses of NaHS was observed, whereas in subjects with CAD, dilation was significantly decreased. B) In "healthy" SD rats with high salt diet (SD HS; 4% NaCl for 3 Days) eliminated H_2S mediated dilation. Inhibition of NOS (L-NAME 10^{-4} M) enhanced dilation at higher doses and blocked negative effect of the HS diet. C) In a model of salt sensitive (SS) hypertension, HS diet had no negative impact on dilation, but NOS blockage still increased H_2S response.* $P<0.05$ one way ANOVA *vs* low salt (LS) n=4-9; # $P<0.05$ vs non CAD control n=4-6.

Figure 2: Differential effect of H_2S in microvasculature.

poorly defined. For example, effective doses used for *ex-vivo* studies of vascular reactivity are several log units higher than those observed in the plasma. The question arises is circulating or tissue H_2S a poor marker of physiological ranges of this gas; and is the effective amounts observed *in vivo* significantly lower than concentrations needed for *ex vivo* or *in vitro* studies? Supporting this theory is the hypothesis that H_2S in plasma may simply be the spillover from its site of synthesis, and hence dose not correlate with cellular relevant doses. Hence we need to carefully consider measuring H_2S concentrations in cell/tissue and correlate these with concentrations where it contributes to physiological changes.

There are clearly many factors contributing to the ongoing debate about physiological effects of H_2S in the vasculature, its site of action, its transport, and its effects on other signaling pathways (e.g., NO). This article attempts to give a brief overview of some of the critical knowledge concerning H_2S in the vasculature. The somewhat unique feature of this gas is that it can serve as a vasodilator and a vasoconstrictor, based on the site and concentration. It would appear that cells exposed to toxic H_2S concentrations can adjust by altering their cellular environment (e.g., changes in gene expression, ROS and ATP production, and states of ion channels). The resulting effects of H_2S on the organ or even the entire animal (including humans) is dependent on the balance of its own signaling and other parameters that work in parallel or opposition of H_2S. These changes will likely result in alteration of H_2S concentrations as well at its rate of production and/or those of other signaling molecules. As the other gasotransmitters NO and CO arguably work in a similar way, the preexisting knowledge of these two ancestors should guide future studies to further the understanding of H_2S physiology.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s)

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