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Hydrogen sulfide and vascular dysfunction: prospects for natural and synthetic donors in clinical applications

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The vascular endothelium acts as a paracrine, endocrine, and autocrine organ that plays a key role in regulating the vascular tone and maintaining vascular homeostasis. Endothelial dysfunctions are characterized by a reduction of the bioavailability of vasodilators (e.g., nitric oxide (NO)) and/or an increase in endothelium-derived contracting factors. These alterations impair endothelium-dependent vasodilation, leading to endothelial activation characterized by proinflammatory, proliferative, and procoagulatory conditions that favor the occurrence of cardiovascular diseases.[1]

Hydrogen sulfide (H_2S) is an endogenous gasotransmitter, such as carbon monoxide (CO) and NO, that relaxes vessels through the adenosine triphosphate-sensitive potassium channel in a calcium-dependent and endothelial-independent manner. However, the activation of the adenosine triphosphate-sensitive potassium channel activation is only one of several pathways through which H_2S modulates endothelial and vascular function. In fact, contrary to NO, which signals mainly through the well-defined soluble guanylate cyclase pathway, H_2S does not act through a single canonical receptor-effector system, leading to more pleiotropic biological effects.

H_2S can be synthesized from L-cysteine or L-homocysteine by cystathionine-γ-lyase (CSE) and cystathionine-β-synthase, and from 3-mercaptopyruvate by 3-mercaptopyruvate sulfurtransferase. Importantly, the expression of these three enzymes can be increased by several stimuli including hypoxia, amino acid restriction, oxidative stress, and inflammation (e.g., by tumor necrosis factor α). It deserves to be pointed out that non-enzymatic (e.g., derived from the reduction of sulfur-containing compounds) and microbiota-derived (e.g., from the gut) sources of H_2S also significantly contribute to systemic H_2S levels.

It is well known that endothelial dysfunction plays a crucial role in hypertension by enhancing contraction and thereby increasing peripheral resistance. Angiotensin II is an important component of the renin–angiotensin–aldosterone system and is a major contributor in regulating blood pressure. However, angiotensin II can induce endothelial dysfunction by impairing endothelial function and inducing smooth muscle cell contraction. In a mouse model of angiotensin II-induced endothelial dysfunction, treatment with the H_2S donor GYY4137 restored aortic expression of sirtuin 6, CSE, and endothelial NO synthase (eNOS), reduced inflammation, and improved vasodilation. Furthermore, H_2S supplementation improved inflammation and endothelial dysfunction in blood vessels of endothelial-specific CSE-deficient mice, demonstrating that H_2S protects endothelial function by activating the sirtuin 6 anti-inflammatory pathway.[2]

In addition to GYY4137, H_2S levels can be increased by L-cysteine and sodium hydrosulfide (NaHS), which can be used as an endogenous and exogenous H_2S donor, respectively. Thus, further research is crucial to better understand the underlying vascular mechanisms at the basis of H_2S-induced vascular benefits.

This perspective aims to summarize the mechanisms through which H_2S can improve vascular dysfunctions to evaluate the role of H_2S as a potential treatment in cardiovascular diseases.

H_2S as a proangiogenic factor: MicroRNAs play a key role in angiogenesis, acting as pro- and anti-angiogenic factors. Among anti-angiogenic microRNAs, miR-640 showed important inhibitory effects by suppressing the migration and tube formation of human umbilical vein endothelial cells. H_2S can also act as a proangiogenic factor. In fact, human umbilical vein endothelial cells treated with NaHS showed reduced miR-640 levels, whereas overexpression of miR-640 attenuated the proangiogenic effect of H_2S. In addition, knockdown of either vascular endothelial growth factor receptor 2 or mechanistic target of rapamycin (mTOR) attenuated the downregulation of miR-640 and the proangiogenic effect induced by H_2S. Moreover, miR-640 bound to the 3′-untranslated region of hypoxia-inducible factor 1α mRNA, inhibiting its expression. Interestingly, the inhibition could be recovered by treating cells with NaHS. Thus, H_2S acts through downregulation of the expression of miR-640 and increasing the levels of hypoxia-inducible factor 1α through the vascular endothelial growth factor receptor 2-mTOR pathway.[3] It has also been demonstrated that H_2S favors angiogenesis through S-sulfhydration and activation of proximal signal transduction components such as vascular endothelial growth factor receptor 2 and eNOS. In fact, S-sulfhydration of vascular endothelial growth factor receptor 2 promotes receptor dimerization and subsequent activation of downstream signaling pathways. Similarly, S-sulfhydration of critical cysteine residues of eNOS stabilizes the enzyme in a dimeric and active state. Moreover, H_2S production is promoted by vascular endothelial growth factor through stimulation of CSE. It was also found that H_2S proangiogenic effects are, at least in part, due to its inhibitory effects on mitochondrial electron transport and oxidative phosphorylation, which leads to increased glucose uptake and glycolytic adenosine triphosphate production.[4]

H_2S modulation by erucin: Vascular inflammation progressively affects the integrity and functionality of the vascular wall, leading to endothelial dysfunction and the onset of several cardiovascular diseases. Erucin is a natural isothiocyanate H_2S-donor derived from *Eruca sativa* Mill, with significant anti-inflammatory effects. Erucin also favors global protein persulfidation, a post-translational modification of L-cysteine residues, thereby improving stress resistance and protecting protein structure and function (e.g., from oxidative damage).

It has been reported that erucin has important anti-inflammatory effects in lipopolysaccharide-exposed human umbilical vein endothelial cells, preserving cell viability and reducing reactive oxygen species and tumor necrosis factor α levels. Erucin also reduced endothelial hyperpermeability by preserving the loss of vascular endothelial-Cadherin. Moreover, it induced eNOS phosphorylation and counteracted lipopolysaccharide-mediated nuclear factor κB nuclear translocation, reducing inflammation.[5] Beneficial effects were also demonstrated with *Eruca sativa* extract, which showed hypotensive effects in hypertensive rats and evoked dose-dependent cardioprotection in an *in vivo* model of acute myocardial infarction.[6] Finally, *Eruca sativa* extract also reduced calcium uptake and apoptotic cell death in isolated cardiac mitochondria,[6] demonstrating an interesting nutraceutical profile on the cardiovascular system, which could be due, at least in part, to its H_2S-releasing properties.

In addition to the previously mentioned effects of erucin and *Eruca sativa* extract as H_2S-donors, it is important to specify that many other natural compounds exhibit significant H_2S-releasing activity, including sulforaphane, several garlic-derived compounds, allyl isothiocyanate, and moringin. Thus, future studies aimed to investigate the H_2S-releasing activity/role of these compounds in endothelial dysfunctions would open a new potential approach in treating cardiovascular diseases.

Role of H_2S in aging and vascular senescence: Aging is a major risk factor for cardiovascular diseases since endothelial senescence occurs, leading to the acquisition of senescence-associated secretory phenotype, where senescent cells cease to divide but remain metabolically active, secreting pro-inflammatory cytokines (such as interleukin 6, interleukin 8, interleukin 1β and tumor necrosis factor tumor necrosis factor α), metalloproteases, growth factors, and extracellular vesicles. Senescence-associated secretory phenotype leads to chronic inflammation and oxidative stress that cause vascular stiffness and endothelial dysfunction, directly contributing to hypertension and cardiovascular diseases.

Interestingly, it has been demonstrated that H_2S levels decrease upon aging and in age-related diseases,[7] suggesting that low H_2S levels in the elderly can significantly increase the risk of cardiovascular diseases. In addition, aging is characterized by a reduction in global protein persulfidation, a well-known protective mechanism. An interesting study found that H_2S concentrations decreased with aging in mouse plasma, heart, liver, kidney, spleen, subcutaneous fat and brown fat, and increased in the brain and lung. Moreover, the expression of H_2S-generating enzymes (cystathionine β-synthetase, 3-mercaptopyruvate sulfur transferase and CSE) was significantly upregulated with the aging process in most of above tissues,[8] suggesting an asynchronous change of H_2S levels and its generating enzymes in most tissues during the aging process.

Aging contributes significantly to cardiovascular diseases and cardiac dysfunction, also by the upregulation of matrix metalloproteinase-9 (MMP-9) expression in the heart tissue, which favors fibrosis and inflammation. Interestingly,

supplementing exogenous H_2S (by NaHS) during aging ameliorated the decline in H_2S concentration in the heart, suppressed MMP-9 expression, and improved the age-associated impairment in cardiac morphology and function. H_2S content in the plasma of healthy human individuals decreased with escalating age, whereas MMP-9 levels increased with age progression. Aging leads to a decrease in H_2S levels in the heart and plasma of mice, severe impairment of cardiac diastolic function, interstitial relaxation, and fibrosis of the heart. Interestingly, supplementation with exogenous NaHS significantly improved these phenomena, maintaining the structure and function of the heart by inhibiting the expression of MMP-9 during the aging process.[9]

Senescent endothelial cells exhibit a reduction in H_2S, eNOS, and peroxisome proliferator-activated receptor δ, coupled with increased inflammatory molecules, sodium glucose transporter type 2 and phosphorylation of signal transducer and activator of transcription 3. These phenomena were reverted by GYY4137 (an H_2S donor). Thus, H_2S ameliorates endothelial dysfunction through the anti-inflammatory effect of the peroxisome proliferator-activated receptor δ/sodium glucose transporter type 2/signal transducer and activator of transcription 3 signaling pathway in senescent endothelial cells and may be a potential therapeutic target for anti-ageing treatment.[10] It has been demonstrated that H_2S delays endothelial senescence by upregulating sirtuin 1 and sirtuin 6 expression.[11,12]

Arterial stiffness, a hallmark of vascular aging, significantly contributes to hypertension and impaired organ perfusion. Vascular smooth muscle cells (VSMCs) dysfunction, particularly VSMC senescence and its interaction with stiffness, is crucial in its pathogenesis. A significant downregulation of CSE expression and H_2S levels was shown in the aortic media during biological aging and angiotensin II-induced aging. The VSMC-specific CSE knockout mice exacerbated angiotensin II-induced aortic aging and stiffness *in vivo* and VSMC senescence and stiffness *in vitro*. Conversely, norswertianolin (a CSE agonist) mitigated these effects. Growth arrest-specific 1 (Gas1) is a crucial target of CSE/H_2S and a downstream target gene of forkhead box protein M1 (Foxm1). Small interfering RNA knockdown of Foxm1 increased Gas1 transcription and reduced the protective effects of H_2S on VSMC senescence and stiffness. Finally, CSE/H_2S sulfhydrates Foxm1 at the C210 site, favoring its nuclear translocation and activity, thus reducing VSMC senescence and stiffness.[13] Thus, endogenous CSE/H_2S reduces VSMC senescence and stiffness, thereby attenuating arterial stiffness and aging, partly through sulfhydration-mediated activation of Foxm1 and subsequent inhibition of Gas1 signaling pathways.

It has been demonstrated that endothelial senescence in naturally aging mice was accompanied by the activation of Nod-like receptor protein 3 (NLRP3) inflammasome pathway, decreased H_2S levels and sirtuin 2 expression/activity. Furthermore, it has been found that endothelial-specific knockout of CSE led to premature aging of blood vessels and increased activation of the sirtuin 2/NLRP3 inflammasome. However, H_2S supplementation (by treatment with GYY4137) significantly improved vascular and endothelial cell function, reducing inflammation and reversing endothelial senescence by decreasing p21, p53, p16, sirtuin 2, and NLRP3 expression.[14] Thus, H_2S could be a new target for improving endothelial aging, offering new treatment/prevention strategies for cardiovascular diseases.

Conclusion and future perspectives: The findings clearly highlight a key role of H_2S in reducing cardiovascular risk, in experimental studies, since this molecule showed an important vasodilator effect by relaxing the smooth muscles of blood vessels, then counteracting hypertension typical of the elderly. Moreover, H_2S showed important antioxidant and anti-inflammatory effects, counteracting oxidative stress and inflammation, two key processes involved in cellular aging and cardiovascular damage, by protecting endothelial cells. H_2S also seems to reduce cardiac hypertrophy and improve diastolic function, counteracting age-related heart muscle stiffness. Finally, H_2S can promote angiogenesis, favoring the formation of new blood vessels.

In summary, maintaining adequate levels of H_2S is crucial to counteract the structural and functional changes that the cardiovascular system undergoes with aging, acting on hypertension, inflammation, and oxidative stress. Additional studies are needed to achieve a higher level of evidence-based medicine, but therapies based on natural or synthetic H_2S donors appear to be promising for future clinical practice. A schematic overview of the multifaceted roles of H_2S in vascular biology and aging is illustrated in **Figure 1**.

The authors declare that no Generative AI was used in the preparation of this manuscript.

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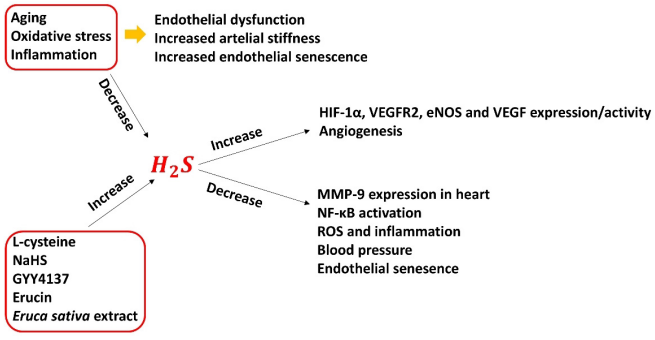

Figure 1 | The H_2S multifaceted roles in vascular biology and aging.
Aging, oxidative stress, and inflammation induce endothelial dysfunction, increase arterial stiffness, induce endothelial senescence and decrease H_2S levels. L-cysteine, NaHS, GYY4137, erucin and *Eruca sativa* extract increase H_2S levels, which can increase angiogenesis (modulating several pathways) and decrease MMP-9 expression, NF-κB activation, ROS, inflammation and blood pressure. Created with Adobe Photoshop (v. 26.0.0). eNOS: Endothelial nitric oxide synthase; GYY4137: a H_2S donor; H_2S: hydrogen sulfide; HIF-1α: hypoxia-inducible factor 1α; MMP-9: matrix metalloproteinase-9; NaHS: sodium hydrosulfide; NF-κB: nuclear factor κB; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor; VEGFR2: vascular endothelial growth factor receptor 2.