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H₂S—The Newest Gaseous Messenger on the Block

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The ability to send and receive signals in vertebrate organisms is a highly dynamic process that maximizes all available substrates to deal with a diverse range of homeo-static perturbations. Typically, one thinks of signals as interactions between and among relatively solid-phase components, such as proteins and lipids within an aqueous (water) milieu. However, an underappreciated signaling class is that of the gaseous transmitters. There are 3 gaseous transmitters: nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H₂S), the newest member of this group. It is thought that although these gases are no longer abundant in the atmosphere, they were major contributors to the evolution of life on Earth, and the ability to generate these gases intracellularly may have evolved over time because of their importance to intracellular processes.¹ The best characterized are NO and CO. NO has been extensively researched and acts primarily as a cardioprotective signaling molecule, induces vasorelaxation and reduces oxidative stress.^{2–4} CO has a more complicated mechanism of action that is highly dose dependent—at physiological doses, CO induces vasorelaxation, but at higher concentrations promotes cardiac toxicity.^{5,6} Traditionally H₂S has been thought of a noxious gas with many toxic effects, but a growing body of evidence indicates that physiologic concentrations of H₂S activate distinct signaling pathways in a variety of cell types that ultimately are protective in the setting of cardiac injury.^{7,8} Some have determined that H₂S is a major constituent of the endothelium-dependent relaxation factor.⁹ In the previous issue of this journal, Kovács et al had extended these mechanistic studies into the clinical arena, and they demonstrated that low plasma H₂S levels predict clinical deterioration in patients with systolic dysfunction, suggesting that H₂S may be emerging as a novel and clinically relevant cardioprotective mediator.

A number of studies in the past 5 years have elucidated the mechanisms by which H₂S functions. H₂S is produced from L-cysteine in vivo by cystathionine γ -lyase (CSE), an enzyme activated via a calcium-calmodulin-dependent pathway after vascular stimulation.¹⁰ CSE-deficient mice have decreased H₂S levels in the heart, serum, and aorta, which leads to marked hypertension and endothelial dysfunction.¹⁰ H₂S acts as a vasorelaxant by opening

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Disclosures

None.

potassium-sensitive adenosine triphosphate [$K^+(ATP)$] channels in vascular smooth muscle cells and similar potassium-sensitive channels in endothelial cells, which leads to closure of voltage-dependent Ca^{2+} channels and reduction of intracellular calcium.^{8,11,12} CSE is localized in the cytosol of vascular smooth muscle cells and translocates to the outer mitochondrial membrane during times of stress, enhancing energy generation (ATP production) by producing H_2S within mitochondria.¹³ It is not yet clear whether H_2S can enhance ATP production within cardiomyocytes. Although CSE is expressed in myocardial tissues and H_2S can be endogenously produced in myocardial tissues, administration is negatively inotropic in mice and may be directly related to $K^+(ATP)$ channel expression on cardiomyocytes.^{14,15} Infusion of H_2S in a porcine ischemic model reduced myocardial energy expenditure and improved catecholamine responsiveness without reducing stroke volume.¹⁶ Reduction in energy expenditure by the heart is an important aspect of beta-blocker therapy, which plays a clear cardioprotective role.¹⁷ Carvedilol increases H_2S levels in the heart and brain, and it may be that some of cardioprotective effects of beta-blockade are related to H_2S production.¹⁸ Interestingly, CSE-deficient mice have increased homocysteine levels, suggesting that homocysteine may be an endogenous substrate used by CSE for H_2S production, and that elevated homocysteine levels, which are associated with increased adverse cardiovascular events, may be related to altered CSE activity and decreased H_2S production.^{10,19}

A number of convincing studies indicate that H_2S is effective in blunting cardiac injury from a diverse group of precipitants. Cardiac-specific overexpression of CSE or exogenous H_2S administration preserves LV systolic function and prevents adverse remodeling/fibrosis after complete myocardial infarction, ischemia-reperfusion injury, pressure overload, or adriamycin-induced cardiomyopathy.^{20–23} The primary mechanism is likely dependent on enhancing mitochondrial function, limiting oxidative stress and reducing cardiomyocyte apoptosis, which in turn lead to decreased inflammatory leukocyte infiltration into the myocardium and pathologic remodeling.^{20,21,24} These cardioprotective effects can be extended to normothermic cardiac arrest and resuscitation with chest compressions, again by preserving mitochondrial function.²⁵

Endothelial cells are important cellular targets of H_2S . Exposure to H_2S leads to increased migration and proliferation through a PI-3 kinase–dependent fashion, significantly improving collateral vessel growth after hind limb ischemia.^{26–28} Aortic segments of CSE-deficient mice have reduced microvasculature density after treatment with the proangiogenic cytokine vascular endothelial growth factor (VEGF), and topical application of H_2S can even improve healing of cutaneous wounds.²⁸

H_2S also promotes increased angiogenesis and production of VEGF after myocardial infarction, which suggests that in addition to mitochondrial stabilization, restoration of blood flow to ischemic tissue may be another key cardioprotective mechanism used by H_2S .²⁹ Interestingly, the ability of H_2S and NO to induce vasodilation and angiogenesis is highly dependent on a direct interaction between these two mediators. For example, disruption of the NO pathway impairs the ability of H_2S to induce vasodilation and angiogenesis, and conversely, disruption of the H_2S pathways impairs the ability of NO to do the same.³⁰

It is unclear as to which form of H₂S is biologically active. Although H₂S is a gas, it has not been given as an inhaled agent in the majority of these studies, but rather H₂S donors (such as sodium thiosulfate) are administered into systemic circulation. When dissolved in aqueous solution, H₂S is weakly acidic and dissociates to form 2 states, HS⁻ and S²⁻.³¹ In addition, thiol complexes can form with other proteins and the effects of H₂S may be indirect. Currently, it is not clear which forms of H₂S (H₂S, HS⁻, or thiol intermediates) are biologically active. Curiously, it has been shown that H₂S and NO interact and form a novel intermediate at physiologic pH, suggesting the possibility of further shared signaling between the 2 gaseous systems.³²

It is surprising how few studies have measured H₂S in a clinical context. Therefore, the publication by Kovač et al is timely in that it provides strong evidence linking H₂S to cardiovascular disease. In a study of children in China, decreased H₂S levels were found to be associated with increased blood pressure, a finding supportive of animal studies.³³ Another study, also of children in China, found that increased levels of H₂S were associated with both vasovagal syncope and postural orthostatic tachycardia syndrome (POTS), and those with POTS had the highest level of any group, suggesting either a primary or a secondary alteration in H₂S levels in those patients who have abnormalities in vascular tone.³³ Interestingly, Kovač et al demonstrate that patients with New York Heart Association (NYHA) functional class IV symptoms have the lowest total plasma sulfide concentrations (analogous to measuring H₂S), which was associated with increased pulmonary artery systolic pressures (PASPs), increased rehospitalization rates, and increased mortality. This effect was independent from other known variables that predict outcome (NYHA, PASP, and pro-B-type natriuretic peptide levels). Another study in children with asthma indicated that those with the lowest levels of H₂S had worsening lung function, and although the authors did not measure PASP, it may be that H₂S levels reflect in part vascular tone within the pulmonary arteries.^{34,35} Although the study by Kovač et al was a small proof-of-principle study, the correlation between mortality and H₂S levels was particularly striking (receiver operating characteristic = 0.904), and it will be very interesting to see if these results can be replicated in a large and diverse group of patients with cardiac dysfunction. These findings are in line with a previous study by the same group, which found that plasma sulfide levels in patients with septic shock are increased and that in animal models, production of H₂S by CSE worsened shock.^{36,37} Together, the data indicate that strategies that promote H₂S production/exogenous administration may be of therapeutic utility and could be explored in highly prespecified patient populations that are clearly “H₂S deficient.”

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