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Hydrogen Sulfide Therapy in Diabetes-Accelerated Atherosclerosis: A Whiff of Success

Diabetes 2016;65:2832–2834 | DOI: 10.2337/dbi16-0042

COMMENTARY

Atherosclerotic cardiovascular disease is the major cause of morbidity and mortality in diabetes (1). Atherosclerosis occurs earlier and with greater severity in the population with diabetes, leading to a much higher risk of myocardial infarction, stroke, and limb ischemia and amputation. Although numerous factors contribute to the etiology of atherosclerosis, oxidative stress and inflammation play a fundamental role and both processes are exacerbated in diabetes. Given the rapidly growing worldwide incidence of diabetes, there is a critical need for new therapies that target atherogenesis and its clinical manifestations in patients with diabetes.

The gasotransmitters nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S) have emerged as crucial regulators of vascular disease in diabetes (2). Although NO and CO have been extensively studied, less is known regarding the role of H_2S in diabetes. H_2S is a colorless, water-soluble gas with the characteristic smell of rotten eggs. It is generated by the metabolism of cysteine by the enzymes cystathionine β-synthase and cystathionine γ-lyase or by the concerted action of cysteine amino transferase and 3-mercaptopyruvate sulfurtransferase (Fig. 1). H_2S is also produced nonenzymatically from glucose, glutathione, thiosulfate, and sulfur-containing proteins and by the bacterial reduction of sulfur in the intestinal tract (3,4). Although long considered a toxic gas, studies in the past decade have revealed important physiological roles for H_2S. H_2S promotes blood flow by dilating blood vessels and inhibiting platelet aggregation (3,5). It also exerts potent antioxidant, antiapoptotic, anti-inflammatory, and angiogenic responses. H_2S elicits many of its biological effects by targeting proteins for *S*-sulfhydration, where sulfur is added to the thiol groups of reactive cysteine residues resulting in the formation of hydropersulfide (6). More recently, H_2S has been shown to mitigate endothelial dysfunction, retinopathy, cardiomyopathy, and nephropathy in experimental animal models of diabetes (7–10), highlighting the protective nature of this molecule.

In this issue, Xie et al. (11) further address the role of H_2S in diabetes and demonstrate for the first time that this gas suppresses diabetes-accelerated atherosclerosis. They show that daily systemic administration of the slow-releasing H_2S donor GYY4137 decreases atherosclerotic lesion size in atheroprone, streptozotocin-induced diabetic mice fed a high-fat diet, independent of any change in circulating blood glucose or cholesterol. The antiatherosclerotic effect of GYY4137 is associated with reductions in macrophage content within the plaque and decreases in the production of superoxide and expression of the adhesion receptors intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in the aortic endothelium. Comparable effects are also observed when peritoneal macrophages or endothelial cells are exposed to high concentrations of glucose and oxidized LDL that mimics the in vivo environment encountered in diabetes. However, the protective actions of GYY4137 are lost if GYY4137 is depleted of H_2S or if a structural analog of GYY4137 that lacks sulfur is used, indicating that H_2S mediates the actions of GYY4137. The authors also demonstrate that GYY4137 activates the transcription factor nuclear factor erythroid 2–related factor 2 (Nrf2) via the specific *S*-sulfhydration of cysteine 151 (Cys151) in Kelch-like ECH-associated protein 1 (Keap1), a repressor protein that binds Nrf2 and promotes its degradation by the ubiquitin proteasome pathway (12). Significantly, deletion or silencing of Nrf2 abolishes the antiatherogenic action of GYY4137 in diabetic mice and cells, illustrating the essential role of Nrf2. In addition, GYY4137 stimulates the expression of heme oxygenase 1 (HO-1) in an Nrf2-dependent manner, and depletion or inhibition of HO-1 abolishes the cellular actions of GYY4137, implicating HO-1 in the antiatherogenic effects of H_2S.

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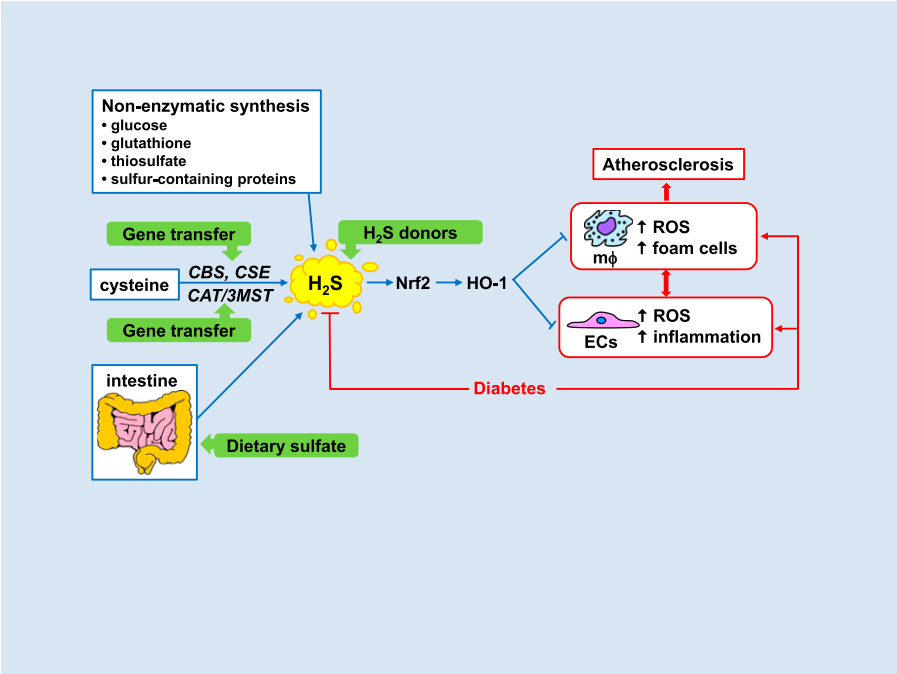

Figure 1—Regulation and function of H_2S in diabetes-accelerated atherosclerosis. H_2S is generated by the metabolism of cysteine by the enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) or by the concerted action of cysteine amino transferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3MST). H_2S is also produced nonenzymatically from glucose, glutathione, thiosulfate, and sulfur-containing proteins and by the bacterial reduction of sulfur in the intestinal tract. Circulating levels of H_2S are depressed in diabetes, but restoration of H_2S via the administration of H_2S donor molecules, gene delivery of H_2S-generating enzymes, and/or dietary sulfate supplementation leads to the activation of the Nrf2–HO-1 signaling axis, which inhibits the development of atherosclerosis by blocking diabetes-induced oxidative and inflammatory stress in endothelial cells (ECs) and reactive oxygen species (ROS) and foam cell formation by macrophages (mϕ).

Notably, Xie et al. (11) detect significantly lower levels of plasma H_2S in diabetic mice that is corrected by the administration of GYY4137. A reduction in circulating H_2S has also been noted in other diabetic animal models and patients with diabetes (7,13–15), supporting the presence of an H_2S deficiency state in diabetes. The cause for this decline is not known but may reflect alterations in the global activity of H_2S-generating enzymes, the liberation of H_2S from other sources, the microbial reduction of sulfate in the intestine, and/or the metabolism of H_2S in diabetes. Clearly, further studies are needed to address this issue and to establish optimal circulating concentrations of H_2S needed to maintain vascular homeostasis in diabetes.

The study by Xie et al. (11) represents an important advance in the field and identifies H_2S as a novel therapeutic target in diabetes-accelerated atherosclerosis. The finding that Nrf2 functions as the initial transducer of the antiatherogenic action of H_2S is somewhat surprising given the controversial role of Nrf2 in atherosclerosis (16), but it is in line with a recent report showing that Nrf2 activation represses atherosclerosis in a mouse model of diabetes (17). The discovery that HO-1 is the downstream target of Nrf2 that mediates the antiatherogenic effects of H_2S in macrophages and endothelial cells is less surprising given the known antiatherogenic properties of its products, biliverdin and CO (18). However, it provides additional evidence that cross talk between signaling gases occurs in diabetes (2), and this may contribute to the vasoprotective actions of H_2S. Moving forward, it will be important to extend this work in male mice to females, as sex differences in the cardiovascular consequences of diabetes exist (19).

A schematic diagram depicting the beneficial actions of H_2S in diabetes-accelerated atherosclerosis is shown in Fig. 1. In this model, restoration of circulating concentrations of H_2S in diabetes leads to the activation of the Nrf2–HO-1 signaling pathway, which limits the development of atherosclerosis by blocking diabetes-induced oxidative and inflammatory stress in endothelial cells and formation of reactive oxygen species and foam cells in macrophages. Several strategies can be used to augment H_2S levels in diabetes. The use of H_2S-releasing compounds is a highly feasible near-term approach. Aside from inorganic salts and natural H_2S donors, many synthetic compounds have been developed that possess superior H_2S release kinetics and pharmacokinetic profiles (20). Alternatively, endogenous circulating levels of H_2S may be increased by gene delivery of H_2S-generating enzymes or by the supplementation of dietary sulfur that is readily converted to H_2S by the gut microbiome. Future

translational studies using these approaches will determine the clinical success of this odorous gas in treating diabetes-associated macrovascular disease.

Funding. W.D. is supported by the American Heart Association Midwest Affiliate (15GRNT25250015).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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