Is H$_2$S a Stinky Remedy for Atherosclerosis?

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Atherosclerosis is a complex and chronic pathological state that adversely affects the structure of blood vessels. Vascular inflammation, endothelial damage, smooth muscle cell migration, foam cell accumulation, and lipid and cholesterol deposition contribute to different stages of plaque formation in large and medium-sized blood vessels. The consequential narrowing and stiffening of blood vessels restricts blood circulation and increases plaque thrombogenicity. Pathogenic causes that lead to these pathological changes in atherosclerosis have always been the center of attention, but we have not yet cleared the cloud on this issue.

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An ancient problem may have an ancient solution. A disease older than the history of mankind, atherosclerosis affects the health of various species in a much more profound fashion than other types of cardiovascular problems. Taking the fish as a case in point, whereas heart failure and hypertension are nonissues with them, fishes spontaneously develop atherosclerosis in their natural habitat regardless of what are on their menu. Even more ancient than the origin of atherosclerosis, production of hydrogen sulfide (H$_2$S) gas by living organisms can be traced far back before the evolvement of the vascular system. Bacteria and archaea produce and use H$_2$S as the essential element for their survival and proliferation. In eukaryotes, H$_2$S is produced under the enzymatic actions of 2 pyridoxal-5'-phosphate-dependent enzymes, cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CSE). Importantly, CSE is a major H$_2$S-producing enzyme in the cardiovascular system.

Recent advance in our understanding of the biological importance of endogenous H$_2$S has shed light on the potential use of this ancient gasotransmitter to deal with atherosclerosis. First, H$_2$S inhibits smooth muscle cell proliferation, one major event in atherosclerosis. Yang et al$^2$ previously reported that, after inhibiting endogenous H$_2$S production by DL-proparglyglycine (PPG) pretreatment or knocking down H$_2$S by short interfering RNA approach, H$_2$S at 50 to 100 $\mu$mol/L induces apoptosis of human aorta smooth muscle cells (SMCs). Without inhibiting endogenous H$_2$S production, exogenously applied H$_2$S at 100 $\mu$mol/L had little effect on SMC apoptosis. The importance of the interaction between exogenous and endogenous H$_2$S is thus indicated. Second, H$_2$S inhibits homocysteine-induced vascular damage. Homocysteine is a key amino acid in regulating cellular levels of cysteine, methionine, and sulfur. Accumulation of homocysteine in the plasma, termed hyperhomocysteinemia, is considered to be an established risk factor for atherosclerosis. Dietary supplementation with methionine and homocysteine induced hyperhomocysteinemia which promoted early atherosclerosis in apolipoprotein E–deficient (apoE$^{-/-}$) mice.$^4$ The development of hyperhomocysteinemia in CSE gene knockout mice has been recently shown.$^5$ It has also been demonstrated that low levels of NaHS (30 or 50 $\mu$mol/L) protected rat aortic SMCs from homocysteine-induced cytotoxicity and reactive oxygen species, leading to improved cell viability.$^6$ Third, H$_2$S reduces atherogenesis. H$_2$S inhibited atherogenic modification of purified LDL induced by hypochlorite in vitro, as measured by apolipoprotein alterations.$^7$ Meng et al reported that during neointimal formation induced by balloon injury in rats,$^8$ CSE expression was reduced and endogenous production of H$_2$S decreased. Rescue of the injured artery with NaHS not only reversed the reduced endothelium-dependent vasorelaxation, but also significantly inhibited neointima formation of the balloon-injured carotid arteries.$^8$

The report by Wang et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology adds a new twist in searching for the direct correlation of H$_2$S and atherosclerosis.$^9$ They found that treatment of apoE$^{-/-}$ mice with NaHS resulted in reduced atherosclerotic plaque, whereas inhibition of CSE activity in apoE$^{-/-}$ mice with PPG enlarged plaque size. By promoting adhesion of inflammatory cells to the endothelium, intracellular adhesion molecule-1 (ICAM-1) may be one of the causative factors for atherosclerosis as its level is significantly higher in human atherosclerotic plaques. Wang et al attributed the antiatherosclerotic effect of NaHS on apoE$^{-/-}$ mice to the reduced ICAM-1 level in circulation and lowered expression of ICAM-1 in aortic endothelial cells.$^9$

The excitement brought by the observation of Wang et al$^9$ is beyond the therapeutic value of NaHS in atherosclerosis, which can be traced back to previous reports.$^{1,8}$ It also proposes challenges and questions. Essential and curious enough for the root of pathogenesis of atherosclerosis is whether abnormality of CSE/H$_2$S system is the cause or consequence of the disease. While showing a marginal decrease in H$_2$S level in plasma from apoE$^{-/-}$ mice having advanced atherosclerosis, basal levels of H$_2$S and CSE protein expression before the manifestation of atherosclerosis in apoE$^{-/-}$ mice were not determined.$^9$ What is even more perplexing is the aortic production rate of H$_2$S and aortic CSE expression level in apoE$^{-/-}$ mice.$^9$ Decreased H$_2$S production rate should reflect decreased CSE activity or expression. The decreased H$_2$S production rate, however, as reported by Wang et al, contradicts with the increased CSE mRNA

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Arterioscler Thromb Vase Biol is available at http://atvb.ahajournals.org

DOI: 10.1161/ATVBAHA.108.180190
expression in aortic atherosclerotic tissues, which cannot be readily explained by an assumed “positive feedback” mechanism.

Interactions between SMCs and endothelial cells are key to atherosclerosis development. Wang et al proposed that H$_2$S produced by SMCs may carry a signal to endothelial cells, thereby altering the production of ICAM-1 and affecting endothelial integrity. This is an interesting concept and worth further comment. Expression of CSE mRNA was initially localized in vascular SMCs, not endothelial cells; however, immunoblot analysis had not been done to detect CSE protein in endothelial cells in earlier studies. As our understanding of the tissue- and species-specific expression of CSE mRNA and proteins deepened, as well as the availability of more specific and sensitive antibodies against CSE that target different CSE protein epitopes, the cellular location of CSE in blood vessel has been better resolved. A recent study by Yang et al presented clear evidence that mouse blood vessels express CSE protein both in vascular smooth muscle and endothelium layers. Cultured HUVECs also express CSE protein and produce H$_2$S. Even in the report by Wang et al, immunopositive staining for CSE seems also obvious in the endothelial layer of mouse aortic tissues from wild-type and apoE$^{-/-}$ mice (see Wang et al, Figure 2). It is therefore likely that H$_2$S produced by endothelial cells has a direct autocrine effect on endothelial cells to regulate ICAM-1 production.

Although a causative role of H$_2$S in the pathogenesis of atherosclerosis is still open for debate and inconsistencies have been encountered, it is clear from this novel study by Wang et al that H$_2$S can be used as an effective therapeutic intervention for atherosclerosis in apoE$^{-/-}$ mice. Stinky but healthy, H$_2$S therapy appears to be a good trade-off. Consumption of garlic, preserved bean curd (stinky tofu), or preserved egg (thousand year’s egg) all increase the production of H$_2$S. But before you put these on the dinner table, pause a while to hold your breath. If there were a “positive feedback” mechanism between H$_2$S and CSE expression as proposed by Wang et al in this issue, application of exogenous H$_2$S to atherosclerotic patients would lead to inhibited CSE expression and decreased endogenous H$_2$S level. Would this be a good news for the prognosis of atherosclerotic patients? Let’s pause even longer and investigate further the correlation between H$_2$S and atherosclerosis.

It ain’t done till it’s done.

Disclosures

None.

References

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Arterioscler Thromb Vasc Biol. 2009;29:156-157; originally published online November 26, 2008;
doi: 10.1161/ATVBAHA.108.180190

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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