Editorial on the Pleiotropic Effects of Hydrogen Sulfide

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The role of hydrogen sulfide (H$_2$S) in the cardiovascular system is under intense investigation with some of its properties gaining acceptance as important in controlling cardiovascular health. This collection of manuscripts outlines several novel and intriguing aspects of H$_2$S signaling and production. Included articles cover a wide range of topics ranging from the benefits of natural product supplements to increase levels of H$_2$S, molecular mechanisms of action and signaling of H$_2$S, systemic and epigenetic effects of H$_2$S on protein express and important limitations on the ability to detect and measure tissue H$_2$S. Together these studies give an excellent overview of some of the important new areas impacted by H$_2$S and other gasotransmitters.

Several studies examined H$_2$S measurement and tissue levels. The work by Sonobe and Haouzi (8) investigates the effect of using different tissue homogenization methods on H$_2$S detection in tissue samples. Studies in heart tissues collected from male rats infused with NaHS or in samples spiked with NaHS observed that all H$_2$S was lost from tissues homogenized at neutral pH within 15 minutes. Furthermore, heart tissues from rats infused with NaHS showed no detectable increase in H$_2$S content until infusions reached toxic concentrations. The authors suggest that infusion of H$_2$S donors in vivo may not detectably raise tissue levels and that the protective effect of H$_2$S donors from the damage of ischemia/reperfusion may be due to a metabolic “preconditioning” effect rather than increases in tissue levels of H$_2$S. Leskova and co-workers investigated thiosulfate effects on sulfide metabolite bioavailability in endothelial cells and how thiosulfate levels regulate redox signaling (3). The introduction includes a good overview of the chemistry and metabolism of thiosulfate, including other potential H$_2$S donors. The focus of this study was to determine how hypoxia affects endothelial cell metabolism of thiosulfates, which are used extensively and safely in human clinical trials for vascular calcification. The report showed that exogenous thiosulfate provides a slow release of H$_2$S under normoxic conditions but this release is blunted during hypoxia. Moreover, the authors found that thiosulfate treatment significantly blunts cystathionine gamma lyase expression revealing a negative
feedback loop controlling endogenous sulfide production. These studies point to the importance of examining cellular metabolism of H$_2$S in order to better understand systemic responses to these compounds.

Several studies have examined protective effects of H$_2$S on vascular and renal function. Li and co-workers examined interactions between estrogen and CSE-dependent H$_2$S generation (5). Their report demonstrates that female CSE-KO mice have lower circulating levels of estrogen and higher levels of atherosclerotic lesions and vascular oxidative stress. The loss of CSE also attenuated the ability of estrogen to rescue the atherosclerotic effects of a high fat diet. The results suggest that protective effects of estrogen on the development of atherosclerotic lesions require an intact CSE system with both the concentration and the location of H$_2$S production critical to the systemic response to estrogen.

Another study by Weber and Sen evaluating H$_2$S inhibition of inflammation reports that the H$_2$S donor, GYY4137, protected mice from an increase in both blood pressure and plasma creatinine during angiotensin II infusion and markedly restored renal blood flow (10). Suppression of miRNA129, a reported regulator of inflammatory cytokines, was linked to the loss of H$_2$S suggesting protective effects of H$_2$S from the inflammatory and hemodynamic sequelae of ANGII-dependent hypertension.

The short review by Fiorucci and co-workers describes regulation of H$_2$S production by bile acids acting on G protein coupled receptors (GPBAR1) (1). This literature review nicely describes putative roles of vasoactive hydrophobic bile acids along with evidence linking activation of G-protein coupled receptors by these factors with increases in both nitric oxide (NO) and H$_2$S production. There have been observations over the past 30 years showing that activation of specific receptors by deoxycholic acid and lithocolic acid lead to vasodilation (7). The authors further discuss how targeting GPBAR1 in conditions such as cirrhotic portal hypertension might lead to novel therapies for the condition.
Another study examining transcriptional regulation of cystathionine gamma lyase found that histone deacetylases (HDACs) suppress CSE mRNA stability and that oxidized LDL impair Ach-induced dilation in part by downregulation of the CSE-H$_2$S system (4). The authors conclude that HDAC inhibitors could be potential therapeutics for atherosclerotic cardiovascular disease and in turn augment cystathionine gamma lyase expression.

Several previous studies have examined cellular mechanisms of H$_2$S. In the study by Swan and colleagues using infused H$_2$S donors, anesthetized rats experienced bradycardia, hypotension and profound apnea. Pharmacological inhibitors were used to determine that H$_2$S may directly inhibit sinoatrial node transmission to slow heart rate independent of vagal tone (9). In the vasculature, work by Naik and colleagues(6) observed that H$_2$S-induced vasodilation in rat mesenteric arterioles appears to involve sulfhydration and activation of endothelial TRPV4 channels with downstream activation of BK$_{Ca}$. H$_2$S-induced dilation was independent of NOS activation but inhibited by blocking TRPV4 channels, BK$_{Ca}$ channels or by removing the endothelium. Evidence of H$_2$S sulfhydration of TRPV4 protein was observed as well as increased TRPV4-dependent localized Ca events in endothelial cells. This novel mechanism provides another way that H$_2$S directly controls vascular tone in small arteries.

The one clinical study in the collection investigated renal sulfate clearance in CHF and healthy patients (2). They observed that sulfate clearance is decreased in heart failure patients and that urinary clearance rates are positively associated with favorable disease outcomes. The mechanism for the improved outcomes with higher sulfate clearance is not clear from this study but the authors speculate that it might reflect higher generation of H$_2$S and upregulation of beneficial metabolic pathways and serve as biomarker and target for therapy.

Together, work in these studies highlights the diverse effects of H$_2$S on multiple systems including the heart, kidneys, liver, vasculature and immune responses. Interactions with other signaling pathways
such as estrogen and bile acid receptors demonstrate H$_2$S exerts both direct signal transduction as well as modulation of multiple endocrine systems. Changes in body levels of sulfates and sulfide pools might impact systemic responses to hypoxia, high fat diets and angiotensin leading to new questions on how dietary sources, environmental exposures and genomic factors influence the systemic response to this newest gasotransmitter.

![Diagram of H$_2$S synthesis and effects](image_url)

**Figure 1:** Hydrogen sulfide (H$_2$S) is synthesized by three different enzymatic pathways and can also be produced non-enzymatically from thiosulfates and other sulfide pools. Target tissues include most systems of the body and articles in this series discuss effects on many of these targets. Additional study is needed to better define H$_2$S signaling in health and disease but it is apparent that this molecule contributes to healthy function of almost all components of the cardiovascular and endocrine systems.


