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Hydrogen Sulfide: The Third Gasotransmitter in Biology and Medicine

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Abstract

The last two decades have seen one of the greatest excitements and discoveries in science, gasotransmitters in biology and medicine. Leading the trend by nitric oxide and extending the trudge by carbon monoxide, here comes hydrogen sulfide (H_2S) who builds up the momentum as the third gasotransmitter. Being produced by different cells and tissues in our body, H_2S, alone or together with the other two gasotransmitters, regulates an array of physiological processes and plays important roles in the pathogenesis of various diseases from neurodegenerative diseases to diabetes or heart failure, to name a few. As a journal dedicated to serve the emergent and challenging field of H_2S biology and medicine, *Antioxidant and Redox Signaling* assembles the most recent discoveries and most provoking ideas from leading scientists in H_2S fields, which were communicated in the First International Conference of H_2S in Biology and Medicine, and brings them to our readers in two Forum Issues. Through intellectual exchange and intelligent challenge with an open-mind approach, we can reasonably expect that sooner rather than later the exploration of metabolism and function of H_2S will provide solutions for many of the biological mysteries of life and pave way for the arrival of many more gasotransmitters. *Antioxid. Redox Signal.* 12, 1061–1064.

The studies of gaseous signaling molecules, gasotransmitters, have made great progress over the last several decades. In 1987, nitric oxide (NO) was discovered as the first endogenously produced gaseous signaling molecule. Carbon monoxide (CO) was identified in the middle of the 1990s as the second one. It appears that the appreciation of the physiological importance of hydrogen sulfide (H_2S), the third gasotransmitter (13), emerged on the scientific horizon only yesterday. Yet we have witnessed one of the most fascinating and fastest expanding research evolutions in the recent history of biomedical sciences. We have seen new scientific publications on H_2S research weekly. We have welcomed new research teams joining the H_2S field monthly.

It was timing. To highlight the explosive and mesmerizing development in the H_2S research field and summarize our updated understanding of the biological and medical implications of H_2S, the first international conference on H_2S in Biology and Medicine was held in Shanghai, China from June 26–28, 2009.

It was exciting. About 160 scientists and trainees attended this meeting from 15 countries and regions. The scientific scope covered by six symposia and poster sessions spanning from cell differentiation and apoptosis, inflammation, glucose metabolism, wound healing, neurodegenerative diseases, cardiac ischemic protection, hypertension, development and reproduction, up to potential human hibernation. The platform provided by this conference allowed researchers to seek interdisciplinary collaboration and translational research effort in H_2S study.

Published in these two Forum Issues of *Antioxidant & Redox Signaling* are examples of the topics and debates that were generated during the conference. The enzymatic basis for endogenous production of H_2S, for example, is case in point. As we know now, H_2S can be produced in a variety of cells, tissues, organs, and systems. Two key enzymes in the transsulfuration pathway, cystathionine β-synthase (CBS) and cystathioine γ-lyase (CSE), have been consistently shown to produce H_2S, pyruvate, and ammonium, using L-cysteine and homocysteine as the substrates (13). In some tissues, both CBS and CSE function to catalyze H_2S production, but in others only one of the two suffices for the production of this gasotransmitter. The existence of additional enzymes in mammalian cells for catalyzing the production of H_2S has been speculated but not substantiated. In this Issue of ARS, Kimura gives a detailed description of 3-mercaptopyruvate sulfurtransferase (3MST). This third enzyme in H_2S production has been identified in brain and vascular endothelium. Using both L-cysteine and alpha-ketoglutarate as substrates, 3MST along

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with cysteine aminotransferase (CAT) produces H_2S. As 3MST is mostly localized in neurons but CBS is in astrocytes, these two enzymes play different roles in regulating brain production of H_2S. In blood vessel wall, 3MST can be found in both vascular smooth muscle cells and endothelial cells, whereas CAT is only localized to vascular endothelial cells. As such, it appears that only vascular endothelium cells in blood vessel wall can use 3MST to produce H_2S since the enzymatic function of 3MST requires the co-existence of CAT.

The role of H_2S in the digestive system under physiological or pathophysiological conditions is another interesting topic, especially given the fact that the gastrointestinal (GI) tract contains the highest concentration of H_2S than any other systems in our body. Sulfur-reducing bacteria in the lumen of the large intestine produce H_2S as high as 3 m*M* through fermentation of sulfur-containing amino acids and intestinal sulfomucin metabolism. GI tissues and cells *per se* also produce H_2S through the action of CBS and/or CSE. As well known, H_2S contributes to the homeostatic control of GI mucosal defence and repair. This protective effect has been ascribed to the anti-inflammatory effects of H_2S, the inhibition of leukocyte adherence to the vascular endothelium, and leukocyte migration to sites of inflammation being examples. If the endogenous production of H_2S from the GI tract is inhibited, as Wallace summarized in his review article in this Issue, the mucosal integrity will be jeopardized and ulcerative and inflammatory diseases of the GI tract would occur (10). While acknowledging some well-studied protective effects of H_2S on the GI tract, another review article by Linden *et al.* in this issue summarizes the current challenges we are facing (8). The regulation of GI production of H_2S is questioned. The target molecules or signaling pathways of H_2S in the GI tract have not been clear. The interaction of bacteria-yielded H_2S and H_2S from the cells of the GI tract and its impact on the CI tract function should be examined. Within the context of the GI tract investigation, Cao *et al.* report in this Issue, for the first time, the expression of both CSE and CBS as well as the endogenous production of H_2S in colon cancer cells and colonic tissues (3). Looking for the endogenous regulation of GI production of H_2S? Butyrate is one of these regulators. Presented in the mammalian colon at high millimolar concentrations, butyrate serves as an energy substrate for colonic epithelial cells, where it is metabolized by mitochondrial β-oxidation. It has been shown that this short chain fatty acid in the GI tract inhibits cell growth and differentiation of several human colon cancer cell lines. Butyrate increases cellular production of H_2S by upregulating the expression of CBS (3). Thus yielded H_2S also reduces the viability of colon cancer cells. Whereas both butyrate and H_2S share the same inhibitory effect on cell growth, these two endogenous substances regulate cancer cell growth through different mechanisms.

Also communicated in this Issue is altered H_2S metabolism in different diseases, including insulin resistance syndrome, hyperhomocysteinemia (HHCy)-induced cardiomyocyte injury, and regional ischemia damages. The report by Chang *et al*. shed light on the interaction of H_2S with methylglyoxal (MG) in vascular smooth muscle cells (VSMCs) (4). Being a metabolite of sugar, protein, and fatty acid, MG is formed in virtually all mammalian cells. Chang *et al.* found that cellular production of H_2S is decreased by MG in a dose-dependent manner in VSMCs. This effect is correlated to the inhibition of CSE by MG. On the other hand, NaHS (a H_2S donor) lowers cellular MG level and decreases MG-induced reactive oxygen species production. Since MG plays a pathogenic role in the development of insulin resistance syndrome, including hypertension, diabetes, and obesity, the involvement of H_2S in these very diseases may be modulated, at least partially, by MG and vice versa. A direct molecule-to-molecule reaction between MG and H_2S would change the structure and function of both involved molecules. It would be interesting to map out the *in vivo* conditions for this reaction to occur and the new molecular structure yielded. The effect of H_2S on HHCy-induced cardiomyocyte damage is reported by Wei *et al.* (14). This study correlated the plasma homocysteine level and endogenous H_2S production with endoplasmic reticulum (ER) stress in cardiomyocytes. The methionine overload-induced HHcy leads to two events in the tested rats, a significant increase in ER stress and a decreased endogenous production of H_2S. Once exogenous H_2S is supplied to these tested animals, cardiomyocytes are rescued from ER stress. Increased ER stress is also observed after endogenous H_2S production is inhibited. Since ER stress is not a patent to HHcy, this study predicts a protective role of H_2S in many other pathological situations in which ER stress is elevated. Whether and how H_2S protects regional ischemia-damaged tissues and organs are examined by Wang M–J *et al.* in this Issue (12). These authors used an *in vivo* hind limb ischemia rat model with unilateral femoral artery occluded for 4 weeks. NaHS supplementation to these animals leads to significant collateral vessel growth, increased capillary density, and improved regional tissue blood flow in ischemic hind limp muscles in comparison with the controls. Increased expression of endothelial growth factor (VEGF) and VEGF receptor 2 and phosphorylation of Akt in ischemic hind limb muscle were also resulted from NaHS treatment. As such, a pro-angiogenic effect of H_2S is indicated. This finding may have significant impact on the management of various ischemic damages to different tissues and organs.

The cytoprotective effects of H_2S against hypoxic and inflammation injuries and the underlying signaling mechanisms are the focus of the next Forum Issue of ARS. Calvert *et al.* present a detailed review on recent discoveries on H_2S-elicited amelioration of *in vitro* or *in vivo* myocardial and hepatic ischemia-reperfusion injury (2). This anti-ischemic protection can be achieved by both applying exogenous H_2S and upregulating the endogenous production of H_2S. In line with this notion, invention of new vehicles to promote endogenous H_2S production can find its important cytoprotective applications. The effects of three novel cysteine containing compounds against rat acute myocardial ischemia are reported in the next Forum Issue (11). These compounds preserve the activities of antioxidant enzymes and reduce the formation of the lipid peroxidation product in ventricular tissues. These beneficial effects are likely mediated by the CSE-catalyzed H_2S production as the inhibition of CSE abolished the protective effects of these three compounds.

In addition to the antioxidant protection, the oxygen-sensing ability of endogenous H_2S would be another mechanism for the cytoprotective effects of this gasotransmitter. The hypothesis that H_2S may be an oxygen-sensing molecule (9), if approved, would fill up a major knowledge gap in our understanding on how the oxygen-sensing cells sense changes in oxygen level and then launch counter reactions to regain a desirable oxygen level. Chemoreceptors and chromaffin cells

are known oxygen-sensing cells in vertebrate cardiorespiratory systems. It is speculated that oxidation of endogenously produced H_2S triggers the cardiorespiratory reflexes and relaxes smooth muscles to increase local blood perfusion and/or ventilation (4). Though this theory is still in the hypothetical stage, lines of supportive evidence have been amounted. Not only hypoxia and H_2S have similar effects on selective types of cells, increased H_2S production augments hypoxic responses. Moreover, H_2S has been shown to be rapidly consumed by O_2 in the range of intracellular/mitochondrial PO_2. Based on these findings, we may need to re-evaluate the regulation of oxygen utilization and mitochondrial function and to add H_2S in the signaling chain for energy production and usage inside the cells.

The challenge facing H_2S researchers can also be well represented by the controversial observations on the role of H_2S in inflammation. In the next Issue of ARS Forum, two articles are specifically devoted to this topic. Bhatia reviews the interaction of H_2S with different inflammation mediators, especially Substance P (1). Based on the observations from his own team and the others on different animal inflammation models, including sepsis and acute pancreatitis, Bhatia believes that H_2S plays a pro-inflammatory role linked to the metabolism of Substance P. On the other hand, the anti-inflammatory effect of H_2S has been reported by many research teams. One explanation for the seemingly opposite roles of H_2S in inflammation resides in the concentration of H_2S being tested and the organs where H_2S is produced as well. Whiteman *et al.* approach this issue from a unique angle (15). These authors examined the effect of a novel H_2S donor (GYY4137) on lipopolysaccharide (LPS)-mediated inflammation. The slow releasing of H_2S from GYY4137 inhibited LPS-induced release of pro-inflammatory mediators and increased the synthesis of the anti-inflammatory chemokine IL-10. The rapid releasing of H_2S from a sulfide salt NaHS at high concentrations, in contrast, increased the synthesis of pro-inflammatory factors. It is concluded that the rate of H_2S generation is important, if not critical, for determining whether H_2S is a pro- or anti-inflammation substance.

As the knowledge base of the metabolism and function of H_2S in our body has been enlarged rapidly over the last decade, more molecular mechanisms underlying the cellular effects of H_2S have been unmasked. K_{ATP} channel is the earliest identified signaling molecular target of H_2S (18). The stimulation of K_{ATP} channels by H_2S has been introduced as the molecular basis for H_2S-elicted cardiac protection (2), blood pressure lowering (17), or insulin release inhibition (16). The mechanism by which H_2S changes K_{ATP} channel function, however, has been a puzzle. Jiang *et al.* have combined the whole-cell patch-clamp technique with a mutagenesis approach to investigate this puzzle (5). They for the first time discovered that H_2S increases K_{ATP} channel currents by specifically interacting with the SUR subunit of K_{ATP} channel complex. Furthermore, they demonstrated that selective cysteine residues located on the extracellular loop of SUR subunit were chemically modified by H_2S. With these observations, the stimulation of K_{ATP} channels by H_2S now can be understood as the consequence of altered configuration of K_{ATP} channel complex. In addition to the stimulation of K_{ATP} channels, H_2S also acts on other ion channels in different types of cells. Li *et al.* report that H_2S inhibits big-conductance calcium-activated K^+ (BK_{Ca}) channels in type I glomus cells of the carotid body (7). It was found that both hypoxia and NaHS decreased the whole-cell BK_{Ca} channel currents significantly and reversibly. Inhibition of CBS activity in type I glomus cells abolished the sensitivity of BK_{Ca} channels to hypoxia. The possibility is thus raised that endogenous H_2S generated by CBS activity may mediate hypoxic modulation of BK_{Ca} channels in chemoreceptor cells.

Exploration of biological importance of H_2S is one of the best examples of how curiosity drives research and innovation. If our fellow researchers and readers become even more curious about H_2S, the purpose of the First International Conference on H_2S in Biology and Medicine and these two related Forum Issues of ARS will have been well served. The unsolved puzzles about the metabolism and functions of H_2S are still many. As food for thought, I will mention some of the puzzles here. The enzymatic reactions leading to H_2S production have not been fully understood. The emergence of 3MST is greatly welcomed but the functional importance of this enzyme in the endogenous production of H_2S remains to be determined. Whether 3MST can produce H_2S under physiological conditions is uncertain, given that its full activity requires an alkaline condition (pH 9.7) (6). Inflammation can be promoted by H_2S and suppressed by the same gasotransmitter. Can we find way to suppress its pro-inflammatory role and enhance its anti-inflammatory role? Increased tissue content of H_2S protects heart from ischemia/reperfusion damage. Meanwhile, high concentration of H_2S has high potential to disrupt electron transport chain in cardiac mitochondrion. One of the intriguing and promising applications of H_2S for cardiac protection is to use it as a preconditioning as well as a postconditioning agent. To score a practical point, a postconditioning appears more feasible than the preconditioning application of H_2S but the effectiveness comparison needs to be conducted. As soon as an oxygen-sensing role is given to H_2S, the questions are immediately asked as why hypoxia and H_2S share the same function if H_2S is a protective factor against hypoxic damage. H_2S releasing can be affected by hypoxia, and so does the function of H_2S. Does H_2S itself have the same or opposite biological affects with different oxidation levels? Or in another word does H_2S lose its cellular effects in the presence of oxygen? Then, let me post the question in everyone's mind—what would be the dividing line between the toxic and physiological levels of H_2S?

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Research on H_2S in biology and medicine is entering its most exciting period. The only way to maintain the momentum and ultimately unmask the importance of H_2S to our health to its fullest is to let curiosity take the lead and let the inspiration to enquire endure. The farewell message on the Whole Earth Catalogs (1974, edition) should be the welcome message in H_2S study: "Stay hungry, stay foolish".

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Abbreviations Used

3MST = 3-mercaptopyruvate sulfurtransferase
BK_{Ca} channel = big-conductance calcium-activated K^+ channel
CAT = cysteine aminotransferase
CBS = cystathionine beta-synthase
CSE = cystathioine gamma-lyase
CO = carbon monoxide
ER stress = endoplasmic reticulum stress
GI tract = gastrointestinal tract
HHCy = hyperhomocysteinemia
H_2S = hydrogen sulfide
K_{ATP} channel = ATP-sensitive K^+ channel
MG = methylglyoxal
NO = nitric oxide
VEGF = endothelial growth factor
VSMCs = vascular smooth muscle cells

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