



Published in final edited form as:

Kidney Int. 2014 June ; 85(6): 1255–1258. doi:10.1038/ki.2013.529.

Hydrogen sulfide to the rescue in obstructive kidney injury

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Abstract

Hydrogen sulfide is a gasotransmitter with far reaching effects on cell function. Studies show that depending on the context hydrogen sulfide can function as an ameliorative agent or as a mediator of kidney injury.

Comment

The primitive Earth atmosphere contained hydrogen sulfide, particularly close to the volcanoes; it appears to have participated in the synthesis of sulfur containing amino acids in abiogenic reactions. Hydrogen sulfide is synthesized by the gamut of living forms, i.e., from bacteria to mammals. However, there was a question on its physiologic relevance unlike the other two gasotransmitters, i.e., nitric oxide and carbon monoxide. Studies in the 1990s suggested that hydrogen sulfide functions as a neuromodulator. Hydrogen sulfide finally achieved recognition as a gasotransmitter of physiologic significance with the discovery that mice lacking cystathionine γ lyase (CSE), one of the enzymes that synthesize hydrogen sulfide, develop hypertension that is ameliorated by sodium hydrosulfide (NaHS), a hydrogen sulfide donor, (1).

Hydrogen sulfide is constitutively produced in mammals by both enzymatic and non-enzymatic pathways (2). Three enzymes are mainly involved in hydrogen sulfide synthesis: CSE, cystathionine β synthase (CBS), and, 3-mercaptopyruvate sulfurtransferase (MST) (Fig. 1). Both CSE and CBS are dependent on pyridoxal phosphate for hydrogen sulfide generation whereas MST is not. CBS catalyzes the generation of cystathionine from L-homocysteine. CSE and CBS promote hydrogen sulfide synthesis from L-cysteine. CSE also catalyzes the conversion of cystathionine to L-cysteine. Coordinated activity of cysteine aminotransferase and MST is involved in sequential generation of 3-mercaptopyruvate and hydrogen sulfide, respectively (Fig. 1). MST is involved in mitochondrial generation of hydrogen sulfide. Non-enzymatic pathways can generate hydrogen sulfide from glucose, thiocystine and thiosulfate (2). Hydrogen sulfide exists in cellular bioavailable pools as free sulfide or as acid labile and bound sulfide (2). Cellular redox status and acidic pH may be able to mobilize hydrogen sulfide from these pools for physiologic actions. Metabolic fate of

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Disclosure: The author declared no competing interests.

hydrogen sulfide includes conversion to thiosulfate, sulfite and sulfate, or, thiocyanate, or, methanethiol and dimethyl sulfide; these reactions are catalyzed by specific enzymes (2). Precise assays for measurement of H₂S in biological samples are currently a subject of debate (2).

Early studies focused on hydrogen sulfide regulation of central nervous system and cardiovascular system. Hydrogen sulfide regulates the actions of N-methyl-D-aspartate (NMDA) receptors in the brain. CSE knock out mice develop hypertension in the absence of changes in eNOS expression; blood pressure is normalized in the CSE^{-/-} mice by the administration of sodium hydrosulfide, a hydrogen sulfide donor, confirming that hydrogen sulfide functions as a vasodilator (1). Nitric oxide and carbon monoxide recruit cyclic GMP for vasodilation. To cause vasodilation hydrogen sulfide hyperpolarizes and opens the K_{ATP} channels. The vasoregulatory effects of hydrogen sulfide are complicated and dose dependent; at lower concentrations hydrogen sulfide functions as a vasodilator while at higher doses it may constrict blood vessels. The interaction among the three gasotransmitters, hydrogen sulfide, nitric oxide and carbon monoxide, is being intensely explored and is likely to be tissue-and cell-specific (3).

Hydrogen sulfide can affect cellular protein function is by sulfhydration. This is a physiologic process by which hydrogen sulfide adds a sulfur to the SH groups of reactive cysteine residues resulting in the formation of hydropersulfide (-SSH); it has been shown to modify a large number of liver proteins affecting their function, e.g., GAPDH. The anti-apoptotic activity of NFκB has been attributed to sulfhydration of p65 unit by hydrogen sulfide (4).

Other physiological properties of hydrogen sulfide include regulation of inflammation, mitochondrial integrity, apoptosis and DNA damage, angiogenesis, and oxidative stress. At the level of tissues and organ systems, hydrogen sulfide integrates several of these mechanisms in a site-specific manner. For example, hydrogen sulfide protects against ischemia reperfusion injury in the heart; the mechanisms appear to involve K_{ATP} channels, mitochondrial integrity and anti-apoptotic actions. In endothelial cells, hydrogen sulfide suppresses high glucose-induced mitochondrial generation of reactive oxygen species and ameliorates endothelial dysfunction (5). Hydrogen sulfide recruits several pathways in serving as an anti-inflammatory molecule including augmenting glutathione production, amplifying actions of superoxide dismutase, and increasing the expression of transcription factor Nrf-2 which promotes expression of antioxidant proteins.

In contrast to its protective effects described above, hydrogen sulfide has also been implicated in mediation of tissue injury. Streptozotocin-induced pancreatic β cell injury involves hydrogen sulfide generated by CSE. Recently, hydrogen sulfide generation by CBS has been implicated in the pathogenesis of colon carcinoma. These data show that actions of hydrogen sulfide vary with the context and are specific to each tissue and situation being investigated.

That the kidney produces H₂S has been known for several decades. Its role in renal physiology and pathology is beginning to be studied. Hydrogen sulfide has been reported to

increase renal blood flow, increase GFR, and, augment urinary sodium excretion possibly by inhibiting the actions of Na-K ATPase and Na-K-2Cl cotransporter. CBS heterozygous knock out (CBS^{+/-}) mice have higher homocysteine level and develop chronic kidney injury. In uninephrectomized CBS^{+/-} mice, supplementation with sodium hydrosulfide ameliorated proteinuria, oxidative stress and apoptosis (6). In rats with streptozotocin induced diabetic kidney injury, sodium hydrosulfide inhibited albuminuria, TGF β expression and matrix accumulation (7). The cellular mechanisms involved in protein synthesis-driven processes such as kidney hypertrophy and matrix accumulation in kidney epithelial cells exposed to high glucose were explored in our laboratory. To induce hypertrophy and matrix protein increment in kidney cells, high glucose inhibits AMP-activated protein kinase (AMPK) that leads to stimulation of mTOR activity and down stream stimulation of mRNA translation, a rate-limiting step in protein synthesis. In renal cells exposed to high glucose hydrogen sulfide restored AMPK activity, leading to inhibition of mTOR, mRNA translation and excessive matrix protein synthesis (8). Together the aforementioned studies suggest that hydrogen sulfide deficiency in the kidney may be a contributing factor for chronic kidney injury.

The role of hydrogen sulfide is more complex in acute kidney injury. Hydrogen sulfide is protective in the ischemia reperfusion model by reducing oxidative stress and inhibition of NF κ B; CSE^{-/-} mice are more susceptible for kidney injury in ischemia whereas sodium hydrosulfide is able to rescue them (9, 10). In contrast, CSE-generated hydrogen sulfide is implicated as a mediator of kidney injury in cis-platinum model of acute kidney injury which was reduced by DL-propargylglycine, an inhibitor of CSE (11). In this issue Song et al have examined the role of hydrogen sulfide in acute kidney injury in unilateral obstruction (12). They found that hydrogen sulfide synthesis was reduced in the obstructed kidney owing to reduction in CBS expression. There was an attempt at compensatory increase in CSE expression which failed to restore hydrogen sulfide generation in the obstructed kidney; the mechanism of these changes in CSE was not explored. Interestingly, there were no changes in the expression of these enzymes in the contralateral unobstructed kidney. Features of obstructive kidney injury, i.e., decrease in cortical thickness, increase in matrix proteins, expression of alpha smooth muscle cell actin, inflammatory cytokine increment and macrophage infiltration, could all be reversed by the hydrogen sulfide donor, sodium hydrosulfide. The agent was effective at a certain dose; a lower dose was ineffective and a higher dose was injurious, which fits with the known therapeutic margin of the gas. It would be interesting to study the fate of NF κ B in this model; hydrogen sulfide could possibly inhibit NF κ B, which would be a departure from the increase in its activity through sulfhydration induced by the gas in mice treated with TNF α (4). In *in vitro* mechanistic studies, hydrogen sulfide inhibited proliferation and differentiation of renal fibroblasts by blocking the activity of TGF β and extracellular signal-regulated kinase (Erk) signaling pathways. There are several unexplored areas in the report by Song which may be considered for future studies. What are the proximal events in obstruction that lead to decrease in hydrogen sulfide generation? Could ROS generated in mitochondria or elsewhere be involved in reduction in CBS expression and hydrogen sulfide generation leading to removal of a constitutive inhibition on inflammation, fibroblast activation and matrix synthesis? Sodium hydrosulfide used in this study provides a proof of principle that

hydrogen sulfide has therapeutic potential in obstructive kidney injury; however, with its notorious rotten egg smell it is unfit for human consumption. There is an urgent need for identifying hydrogen sulfide donors that can be explored for therapeutic effects in human subjects.

In summary, hydrogen sulfide is the new molecule on the block that has the potential to either harm the kidney (e.g., cis-platinum injury) or help the kidney (obstructive and ischemic renal injury), which emphasizes that context is critical in evaluation of its role. The machinery for constitutively synthesizing hydrogen sulfide is present in various parts of the nephron. Since it seems to affect ROS generation, inflammation, DNA synthesis, apoptosis and synthesis of proteins including matrix proteins, hydrogen sulfide deserves investigation for its role in the whole spectrum of kidney disease.

Acknowledgments

Supported by funds from NIH and VA Research Service. The author wishes to thank Dr. C. Kevil and Dr. G. G. Choudhury for critical reading of the manuscript and helpful suggestions.

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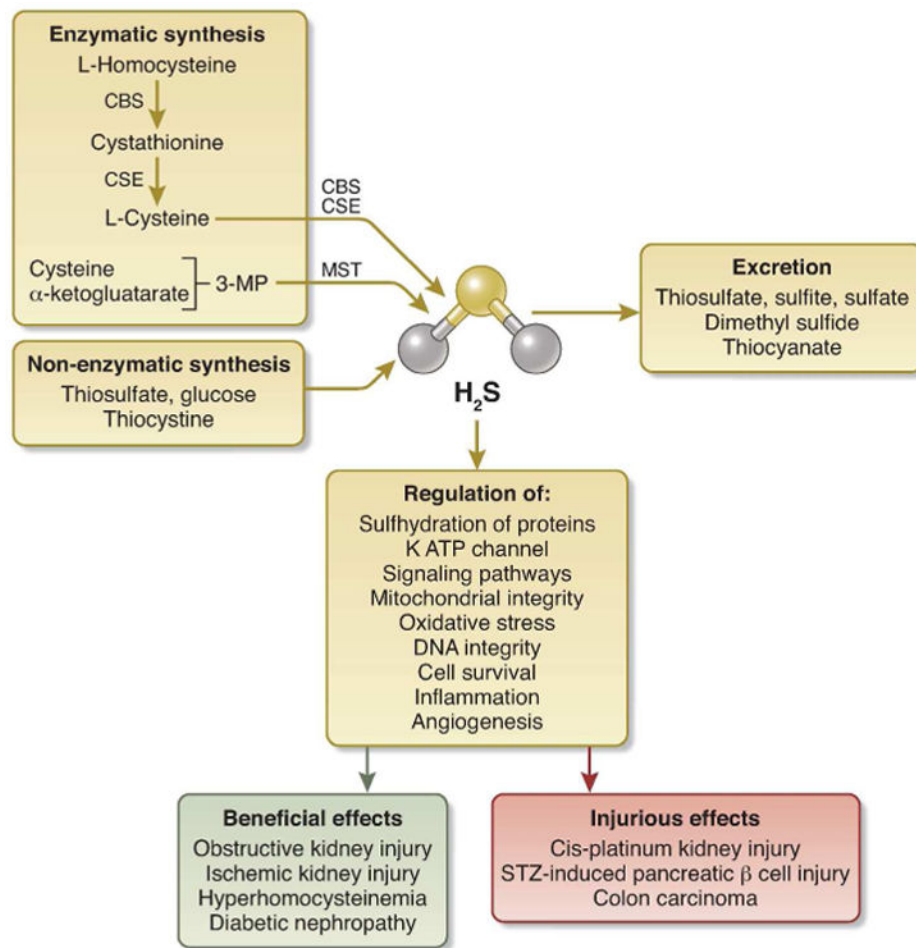


Figure 1. Hydrogen sulfide - synthesis, degradation and cellular effects 142×145mm (600 × 600 DPI)