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Review

Hydrogen sulphide and the kidney: Important roles in renal physiology and pathogenesis and treatment of kidney injury and disease

I. Lobb [a,b], E. Sonke [b,c], G. Aboalsamh [b,d,e], A. Sener [a,b,d,e,*]

[a] Department of Microbiology and Immunology, Western University, London, Ontario, Canada
[b] Matthew Mailing Center for Translational Transplant Studies, London Health Sciences Center, Western University, London, Ontario, Canada
[c] Department of Anatomy and Cell Biology, Western University, London, Ontario, Canada
[d] Department of Surgery, Western University, London, Ontario, Canada
[e] Multi-Organ Transplant Program, London Health Sciences Center, Western University, London, Ontario, Canada

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ABSTRACT

The kidney is an essential mammalian organ that serves to filter toxins and metabolic by-products out of the blood, which are then excreted through urine. Hydrogen sulphide (H_2S) is a recently characterized, endogenous gaseous molecule with important physiological roles. Many interesting roles continue to be identified for H_2S related specifically to the kidney. The current review discusses how production and action of H_2S influences normal physiology of the kidney. We investigate as well the many roles H_2S plays in the pathogenesis and treatment of kidney injury and disease, such as chronic kidney disease (CKD), ureteral obstruction (UO), hyperhomocysteinaemia (HHcy), drug-induced nephrotoxicity (DIN) and renal ischaemia reperfusion injury (IRI). We suggest that H_2S plays a complex and essential role in the normal function of the kidney and dysregulation of H_2S production can directly or indirectly contribute to the pathogenesis of renal disease and injury. Also, H_2S could be a promising potential therapeutic treatment to decrease the severity of several renal diseases. Further research will identify increasingly important and complex roles for H_2S in renal physiology and how H_2S can be effectively utilized to improve clinical outcomes of renal disease.

Contents

* Corresponding author. Department of Surgery, Western University, University Hospital, C4-208, 339 Windermere Road, London, Ontario, Canada N6A 5A5. Fax: (1)519-663-3858.
E-mail address: alp.Sener@lhsc.on.ca (A. Sener).

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1. Introduction: hydrogen sulphide as a mammalian signalling molecule

The physiological relevance of hydrogen sulphide (H_2S) first became apparent in 1996, when it was observed to modulate N-methyl-D-aspartate (NMDA) receptor-mediated functions in the hippocampus [1]. We now know that in addition to serving its role as a neuromodulator of long term potentiation, H_2S is produced systemically and serves pleiotropic functions within the cardiovascular system, kidneys, liver, pancreas, gastrointestinal system, urinary system and reproductive system [2–8]. The enzymes responsible for H_2S synthesis – cystathionine-beta-synthase (CBS), cystathionine-gamma-lyase (CSE) and 3-mercaptopyruvate sulphurtransferase (3-MST) – have been reported to be ubiquitously expressed in the majority of human cell types to varying degrees. Correspondingly, H_2S is thought to be in the nanomolar to micromolar range within the blood, further solidifying the claim of H_2S as a physiologically relevant gaseous molecule [9].

H_2S has been shown to alter the activity and expression of proteins from multiple signalling pathways involved in apoptosis, inflammation, angiogenesis, proliferation, metabolism, oxygen sensing and oxidative stress. Whether the production of H_2S is finely regulated in order to exert specific cellular responses is still up for debate; however it is clear that this gaseous molecule is at least serving as a homeostatic sensor capable of regulating several aspects of cellular physiology [10]. H_2S is able to alter cellular physiology in a variety of ways which are as diverse as the downstream effects that are induced. Such mechanisms include; (i) regulation of kinase, transcription factor and ion channel activity via post-translational S-sulphhydration of cysteine residues and through the production of polysulphides (ii) binding of haeme in haeme-containing proteins, (iii) scavenging of reactive oxygen species (ROS) and (iv) donation of electrons to the mitochondrial electron transport chain (ETC) to fine tune bioenergetics [3,11–13]. With such a wide array of functions, it is not surprising that disruption of endogenous H_2S synthesis has been implicated in pathologies such as Alzheimer's Disease, Down Syndrome, hypertension, cancer, chronic kidney disease (CKD), diabetes and aging [9]. Despite the fact that research on this molecule is still in its infancy, the therapeutic value of exogenous sources of H_2S is already beginning to be investigated [14]. In addition to being investigated in the context of the diseases outlined above, H_2S has been shown to attenuate ischaemia reperfusion injury (IRI) resulting from myocardial infarction as well as during organ transplantation [15–18].

In this review, we will focus on the progress that has been made in understanding the role H_2S serves in the kidney. Specifically we will explore how H_2S plays a role in (i) normal renal physiology, (ii) the pathophysiology of CKD and its co-morbidities, (iii) nephrotoxicity and (iv) attenuating IRI during renal transplantation.

2. Hydrogen sulphide in normal renal physiology

While a physiological role for H_2S was not documented until 1996, the production of H_2S in mammalian tissue was originally documented by Stipanuk and Beck in 1982 [19]. In addition to the liver, brain, heart and skeletal muscle, they identified the kidneys as a major producer of H_2S, concluding that under physiological conditions all three enzymes are involved in H_2S production, with CSE being the major contributor [19]. While the authors did not characterize the localization of these enzymes within the kidney, further work eventually established that CBS, CSE and 3-MST are primarily present in proximal tubules within the renal cortex [20–22]. More recently, it has been noted that CBS primarily localizes to the proximal convoluted tubule in the outer cortex whereas CSE localizes most prominently to the proximal straight tubule in the inner cortex as well as to the outer medulla [23,24]. One possible explanation for the difference in localization of CSE and CBS is that CSE is required for the catabolism of cysteine that arises from glutathionine synthesis in the proximal straight tubule of the nephron [20]. An additional observation by Ishii et al. illustrates that CSE expression is strongly induced in the proximal straight tubule during murine development and then regresses to 50% of its peak expression, suggesting a possible role for CSE in facilitating development of the nephron [23].

While it has long been known that the H_2S-producing enzymes are essential in the kidney due to the role they play in metabolizing homocysteine (Hcy), a functional role for H_2S itself in normal kidney physiology was only recently investigated [4]. Using an intrarenal arterial infusion model in rats, Xia et al. demonstrated that both CSE and CBS are involved in regulating baseline haemodynamics and tubular properties, with renal H_2S concentrations correlating with increased renal blood flow (RBF), glomerular filtration rate (GFR), urinary excretion, natriuresis and kaliuresis [4]. Possible mechanisms of the renal actions of H_2S could include induction of vasodilation in the case of increased RBF and GFR, and inhibition of the tubular Na^+/K^+ ATPase (NKA) and the $Na^+/K^+/2Cl^-$ Co-transporter (NKCC) in the case of natriuresis and kaliuresis [4]. Baseline renal H_2S production may also control the renin–angiotensin system (RAS), either directly by altering cAMP production, or indirectly via regulation of ROS, possibly affecting global hemodynamic parameters [25,26]. Thus, it is possible that renal H_2S production may be a homeostatic cellular response to changes in physiological parameters, though further investigation is required to identify which alterations to the physiological balance elicit renal H_2S production.

Although various studies have shown that glomerular injury can be attenuated through H_2S therapy [27,28], H_2S-producing enzymes are noticeably lacking in glomerular epithelial cells [22–24]. It has recently been observed that baseline expression of H_2S in glomerular epithelial cells (GECs) may be important in regulating global protein synthesis through AMP-activated protein kinase (AMPK) and mammalian target of rapamycin complex 1 (mTORC1). Given the membrane permeability and paracrine nature of H_2S, it is possible that production of H_2S in nearby proximal tubular epithelial cells or vascular endothelium could be sufficient for the needs of GECs, thus making it unnecessary for H_2S to be produced in the glomerulus itself [28]. Similarly, proximal tubule capillaries (PTCs) have been observed to vasodilate in response to exogenous H_2S while they themselves do not express CBS nor CSE. Given the lack of smooth muscle cells in these capillaries, it was speculated that proximal tubule-derived H_2S also regulates the diameter of these structures [22].

As in many other organ systems, the role of H_2S as a modulator of the renal oxidative stress response has been widely noted. This occurs through both upregulation/potentiation of antioxidants like Nrf-2, superoxide dismutase (SOD), catalase, glutathionine, apocyanin and N-acetyl-L-cysteine, and through down-regulation of ROS-generating enzymes such as NADPH-oxidase [29]. In addition, D'Araio

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