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Hydrogen sulfide, then nitric oxide and vasoprotection

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Vascular dysfunction is typically associated with hypertension and contributes to the progression of cardiovascular disease. Altered vascular tone that constitutes an exaggerated vasoconstrictor response or an attenuated ability for vasorelaxation may potentially lead to a chronic increase in vascular resistance and an elevation in blood pressure. A key component regulating vascular tone is the nitric oxide (NO) system whereby activation of NO synthase (NOS) generates NO; the most prominent NOS isoform in the vasculature is endothelial NOS (eNOS or NOS type III) [1,2]. A well characterized signaling pathway for NOS activation and NO release is the PI3 kinase–Akt kinase axis that results in phosphorylation of the Ser^{1177} residue of eNOS for assembly and activation [2]. Subsequent release of endothelial NO activates soluble cGMP cyclase in the smooth muscle to form cGMP, an essential cofactor for protein kinase G (PKG). The activation of PKG leads to the phosphorylation of multiple substrates that facilitates vasorelaxation [3,4]. The importance of the NO system in blood pressure regulation reflects in part, the sustained hypertensive response to administration of NOS inhibitors such as L-NAME or the targeted deletion of eNOS, as well as the loss of NO tone in various forms of hypertension and other cardiovascular diseases [1,5].

In a very extensive study comprising both hypertensive patients and a preclinical model of renovascular hypertension, Xia *et al.* [6] sought to establish the contribution of another gas molecule hydrogen sulfide (H_2S) to vascular tone. They report that the H_2S system resides upstream of NOS/NO and identify the signaling pathways for H_2S in the endothelium [6]. The authors assessed two cohorts with established hypertension and normal blood pressure with respect to circulating H_2S levels and the vascular response to H_2S in isolated renal arteries from both groups. Additional studies determined the influence of exogenous H_2S on blood pressure and vascular reactivity in the Goldblatt model (two-kidney, one-clip) of renovascular hypertension. The study established that both clinical and experimental hypertension were associated with significantly lower levels of circulating H_2S [6]. In the human renal arteries, protein levels of the H_2S-generating enzyme cystathionine γ-lyase (CSE) were also lower in the hypertensive vessels that appear to reflect an attenuated synthesis of the enzyme. Moreover, H_2S exposure (12 h) of the isolated renal arteries from the patients with hypertension reversed the decline in CSE expression suggesting a

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Conflicts of interest

There are no conflicts of interest.

positive feedback role of H_2S to maintain vascular synthesis. Of particular interest, H_2S exposure attenuated protein and mRNA expression of the angiotensin-II type-1 receptor (AT_1R), a novel mechanism to preserve vascular function in the presence of an activated renin–angiotensin–aldosterone system (RAAS). H_2S exposure also restored the attenuated acetylcholine (Ach)-dependent response of the renal vessels from the hypertensive group. Restoration of the Ach response by H_2S was associated with augmented levels of the peroxisome proliferator activator receptor (PPARδ), as well as an increase in phosphorylated eNOS, Akt and AMP kinase [6]. The link to NOS–NO signaling was corroborated in human endothelial cells; exogenous H_2S restored NO levels following Ang-II exposure and addition of selective inhibitors/antagonists to PI3 kinase, Akt, AMP kinase and PPARδ reversed the NO response following H_2S treatment in these cells [6].

In the renovascular hypertensive rats, circulating levels of H_2S were reduced over 70% and protein expression of CSE was similarly reduced in the renal vessels. Exogenous treatment partially reversed the increase in mean arterial pressure; however, this was apparent only after 12 weeks of H_2S treatment and continued to the end of the study at 20 weeks. The lag time for H_2S to lower blood pressure was not addressed in the study and it is unclear whether this reflects effects on the endogenous H_2S system or other regulatory systems within the vasculature. In this regard, the reduction in blood pressure by H_2S was associated with lower AT_1R expression, but higher CSE levels may infer a restored capability for local H_2S formation to impact the vascular RAAS [6]. Moreover, chronic H_2S treatment restored the blunted Ach response in the isolated vessels of the hypertensive rats. Blockade of PI3, Akt and AMP kinases, as well as NOS and PPARδ again abrogated the protective effects of H_2S administration that suggest that the vascular actions of H_2S are primarily mediated by NO. The preservation of NO tone by the chronic administration of H_2S is consistent with the downregulation of the AT_1R in lieu of the inhibitory effects of NO on various components of the RAAS. Furthermore, the chronic administration of a PPARδ agonist reduced blood pressure in spontaneously hypertensive rats (SHR); the PPARδ agonist also reduced indices of inflammation (TNFα, IL-1β, ICAM-1, IL-6) and attenuated the constrictor effects of Ang II and endothelin-1, but did not lower mRNA levels of the AT_1R or the ET_AR [7].

The current data revealing that the vascular effects of H_2S lie upstream from the generation of NO contrast with the reported direct effects of H_2S to either enhance vasorelaxation or stimulate vasoconstriction. The direct vascular effects of H_2S appear to be dependent on the concentration of H_2S applied to the vessel; application of H_2S at doses less than 30 μmol/l are constrictive whereas concentrations greater than 100 μmol/l stimulate relaxation of the vessel [8,9]. The direct constrictor actions of H_2S appear to be mediated through a reduction in NO and an increase in oxidative stress [8–10]. In contrast, higher H_2S concentrations induce activation of K_{ATP} channels that may reflect an increase in intracellular calcium levels to elicit direct vasorelaxant effects [9,11]. The current data support past studies that assessed the chronic effects of H_2S on blood pressure and vascular function in various models of hypertension. Blood pressure-lowering effects of H_2S were previously reported in the spontaneously hypertensive rat (SHR), DAHL salt-sensitive rat and chronic Ang II-infused mice; the effects of H_2S in these studies were associated with a reduction in oxidative stress in the vasculature [12]. Tissue-wide deletion of the H_2S-generating enzyme CSE was also associated with a marked increase in blood pressure, as well as evidence of

vascular dysfunction [12]. Although the current study did not assess the effect of acute (12 h) or chronic (20 weeks) H_2S treatment on vascular redox balance, stimulation of NO tone by H_2S may also reflect an increase in NO bioavailability via the activation of scavenging enzymes to lower oxidative stress or direct interactions with NO to form novel hybrid forms [8,10,13].

The present results demonstrate a significant vasoprotective effect of H_2S that may contribute to the blood pressure-lowering actions of this molecule in renovascular hypertension. Although this study on the cardiovascular role of H_2S primarily focused on the vascular actions of the molecule, H_2S exerts significant actions on the heart as well [9,14]. Indeed, H_2S has direct actions on the cardiomyocyte that involve NO signaling and mitochondrial protection to preserve cardiac function [2,15]. Moreover, there is evidence for the role of H_2S in other cardiovascular-relevant tissues such as the brain, kidney, gut microbiome and immune cells; and these targets should be continued areas of investigation, particularly the extent for the NO-dependent and NO-independent actions of H_2S [9,10,12]. Finally, the study by Xia and colleagues documented that the H_2S effects likely involve the downregulation of the AT_1R in both hypertensive patients and experimental hypertension, but the impact of H_2S tone on the alternative ACE2–Ang-(1–7)-AT_7–MasR axis that functionally opposes the ACE-Ang II-AT_1R should be evaluated as well [5].

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