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# COMMENTARY

# What is the significance of vascular hydrogen sulphide ($H_2S$)?

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The important role of nitric oxide (NO) in the regulation of vascular tone has been well studied. By contrast, the vascular significance of another gaseous mediator, hydrogen sulphide ($H_2S$), is still poorly understood. A study published in this issue of the *British Journal of Pharmacology* now provides evidence that in addition to the vasorelaxant effects of $H_2S$ reported *in vitro*, low concentrations of $H_2S$ also cause arterial vasoconstriction, reverse NO-mediated vasorelaxation and cause an NO-dependent pressor effect *in vivo*. This commentary discusses the implications and questions raised by these results.
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Hydrogen sulphide ($H_2S$) is endogenously generated from cysteine in a reaction catalysed (in the vasculature) by cystathionine $\beta$-synthase. Unlike the endogenous gas nitric oxide (NO), the physiological relevance of $H_2S$ is unclear, although under much investigation. In a continuation of recently published work showing that $H_2S$ reacts chemically with NO to produce an as-yet unidentified nitrosothiol *in vitro* (Whiteman *et al*., 2006), Ali *et al*. (2006) now report the physiological consequences of such an interaction. In the present study, low, physiologically relevant (*ca*. 50 $\mu$M in rat and human plasma) concentrations of $H_2S$ cause endothelium-dependent, $CuSO_4$-sensitive ($CuSO_4$ converts nitrosothiols to nitrites and nitrates) arterial vasoconstriction, suggested to be owing to quenching of NO. Furthermore, $H_2S$ reversed NO-mediated vasorelaxation to acetylcholine and histamine in a $CuSO_4$-sensitive manner. The conclusion drawn from these data is that formation of a nitrosothiol compound terminates the biological activity of NO.

To date, $H_2S$ has been shown to cause vasorelaxation of rat isolated aortae (Zhao *et al*., 2001), albeit at relatively high concentrations ($EC_{50}$ 125 $\mu$M) which appear to be more consistent with the levels of $H_2S$ stimulated by situations such as sepsis, shock and inflammation (levels of 150 $\mu$M plasma $H_2S$ have been reported in humans with septic shock, Li *et al*., 2005). The vasorelaxant effects of $H_2S$ *in vitro* are largely thought to be owing to activation of potassium channels (Zhao *et al*., 2001; Cheng *et al*., 2004). Consistent with the current literature, the present authors (Ali *et al*., 2006) show that high concentrations of $H_2S$ (200–1600 $\mu$M) cause $K_{ATP}$ channel-mediated vasorelaxation; however, at low concentrations (10–100 $\mu$M), they find a vasoconstrictor effect of $H_2S$. It is of note that other studies of $H_2S$ in the vasculature have not revealed a vasoconstrictor response to $H_2S$ in these concentration ranges (Zhao *et al*., 2001; Cheng *et al*., 2004). Additional studies are therefore required to establish whether this newly reported effect of $H_2S$ is potentially a species, strain and/or vascular bed-sensitive response. Indeed, Dombkowski *et al*. (2005) report that $H_2S$ causes both vasorelaxation and vasoconstriction in different arteries from a range of vertebrates including shark, hagfish, sea lamprey, toad, alligator, duck and rat. These authors suggest that $H_2S$ is a versatile vasoregulatory molecule that can be used to suit both organ-specific and species-specific requirements.

The major question raised from these interesting data is: what are the physiological or pathophysiological consequences of such a reaction? As both NO and $H_2S$ are increased by sepsis and inflammation, an initial suggestion might be that the reaction of the two compounds might act as a braking mechanism to prevent exaggerated vasodilatation and large decreases in peripheral resistance. Thus, are the cardiovascular responses to sepsis enhanced if we block $H_2S$ production? Does administration of $H_2S$ reverse the depressor response to sepsis? Data presented by Ali *et al*. (2006) would certainly suggest that $H_2S$ could be beneficial by quenching the effects of NO under these conditions. However, conversely, in a rat model of haemorrhagic shock, inhibitors of $H_2S$ biosynthesis were found to partially restore blood pressure (Mok *et al*., 2004). Furthermore, in lipopolysaccharide (LPS) models of sepsis, it has been reported that pretreatment with $H_2S$ significantly inhibits the LPS-induced increase in inducible NO synthase expression (with additional decreases in nuclear factor-kappa B, Oh *et al*., 2006), and vice versa, that the NO donor nitroflurbiprofen, downregulates the biosynthesis of $H_2S$ (Anuar *et al*., 2006).

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Therefore the pro- versus anti-inflammatory actions of $H_2S$ are far from understood.

The authors of the present study found that slow infusion of a low dose of $H_2S$ ($10\,\mu mol\,kg^{-1}$) caused a small, NO-dependent pressor effect in anaesthetized rats, but high doses ($25\,\mu mol\,kg^{-1}$) caused a depressor effect. Previously, a depressor effect of infused $H_2S$ has been reported in anaesthetized rats ($3–14\,\mu mol\,kg^{-1}$, Zhao *et al*., 2001). Clearly, the effects of $H_2S$ are of potential significance in terms of therapeutic manipulation of blood pressure, and therefore it would be of interest to know what might be the cardiovascular effects of both chronic inhibition/administration of $H_2S$. As cardiovascular disease is often associated with dysfunctions of NO, are there also dysfunctions of the $H_2S$ system? And what are the effects of $H_2S$ manipulation in these conditions? Preliminary evidence suggests that $H_2S$ may be decreased in patients with coronary heart disease, hypertension and those who smoke (Jiang *et al*., 2005). Interestingly, this is to a level (to $\sim$25 vs 50 $\mu$mol/l $H_2S$) at which the present authors would suggest $H_2S$ terminates the biological activity of NO. Does this cause the reduced bioavailability of NO often observed with these patients, or does this exaggerate a pre-existing problem?

The authors of the present study suggest that nitrosothiols are formed from $H_2S$ and NO (terminating NO activity), but it is not suggested what subsequently happens to these compounds. Allen and Piantadosi (2006) describe a process whereby NO is actually protected as a nitrosothiol bound to haemoglobin in red blood cells such that $O_2$-dependent allosteric modulation of haemoglobin releases the NO to cause local vasodilatation. Similarly, Chvanov *et al*. (2006) have shown that NO can be released from nitrosothiols in a calcium-dependent manner upon acetylcholine stimulation in isolated pancreatic acinar cells. Thus in some circumstances, NO can be re-released from nitrosothiols, which warrants further investigation in the context of the present data. Perhaps the 'physiological' role of $H_2S$ lies in its ability to store and quickly release (independent of enzymatic activity) NO via nitrosothiols?

In conclusion, there appear to be distinct vascular actions of $H_2S$ in the rat aorta at low (vasoconstriction and pressor effects) and high concentrations (vasorelaxation and depressor effects), with interactions and cardiovascular consequences between $H_2S$ and NO. The roles of $H_2S$, NO and nitrosothiols in both normal physiology and pathophysiology appear intriguing and complex, and the present study by Ali *et al*. (2006) opens many new lines of research for both NO and $H_2S$.

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