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NO-H_2S interactions involve cGMP

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Background

Hydrogen sulfide (H_2S) and nitric oxide (NO) have been recognized as endogenous signaling molecules, involved in a variety of homeostatic and disease processes. Although it is well-established that NO increases cGMP content of cells and tissues by activating soluble guanylyl cyclase (sGC), the ability of H_2S to affect cyclic nucleotides levels has been controversial.

Results

We have shown that H_2S increases cGMP in both endothelial and smooth muscle cells. However, H_2S does not activate sGC or alter NO-induced sGC activity. Interestingly, H_2S inhibits phosphodiesterase (PDE) activity; although it reduces PDE activity of several PDE H_2S is most effective and potent against PDE-5. IN line with the ability of H_2S to increase cellular cGMP, we observed that exposure of cells to H_2S leads to activation of cGMP-dependent protein kinase and VASP phosphorylation. As both NO and H_2S promote angiogenesis and vasodilation we explored their interactions in the vessel wall in the context of these two biological processes. Inhibition of eNOS or PKG reduced the H_2S-stumlated angiogenic properties of endothelial cells, as well as H_2S–stimulated vasorelaxation, suggesting a prominent role for cGMP/PKG pathways in H_2S signaling. On the other hand, silencing of the H_2S-producing enzyme cystathionine-γ-lyase (CSE) reduced NO-stimulated cGMP accumulation, angiogenesis and smooth muscle relaxation, proving that NO requires H_2S to manifest its effects. Finally, H_2S-induced wound healing and angiogenesis in vivo was suppressed by pharmacological inhibition or genetic ablation of eNOS.

Conclusion

Inhibition of the production of one gasotransmitter (NO or H_2S) reduces the ability of the other to elevate cGMP and to trigger angiogenesis and vasodilation. These observations establish the existence of a positive, synergistic cross-talk between H_2S and NO in vascular tissues.

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