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ORAL PRESENTATION

NO-H₂S interactions involve cGMP

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From 6th International Conference on cGMP: Generators, Effectors and Therapeutic Implications Erfurt, Germany. 28-30 June 2013

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 H₂S increases cGMP in both endothelial and smooth muscle cells. However, H₂S does not activate sGC or alter NO-induced sGC activity. Interestingly, H₂S inhibits phosphodiesterase (PDE) activity; although it reduces PDE activity of several PDE H₂S is most effective and potent against PDE-5. IN line with the ability of H₂S to increase cellular cGMP, we observed that exposure of cells to H₂S leads to activation of cGMPdependent protein kinase and VASP phosphorylation. As both NO and H₂S 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 H₂S-stumlated angiogenic properties of endothelial cells, as well as H₂S-stimulated vasorelaxation, suggesting a prominent role for cGMP/ PKG pathways in H₂S signaling. On the other hand, silencing of the H₂S-producing enzyme cystathionine- γ -lyase (CSE) reduced NO-stimulated cGMP accumulation, angiogenesis and smooth muscle relaxation, proving that NO requires H₂S to manifest its effects. Finally, H₂Sinduced wound healing and angiogenesis in vivo was suppressed by pharmacological inhibition or genetic ablation of eNOS.

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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.

Acknowledgements

Much of the above-mentioned work has been done through collaborative efforts in the context of the European Network of Gasotransmitters (COST-BM1005) that is funded through the European Science Foundation.

Published: 29 August 2013

doi:10.1186/2050-6511-14-S1-O32 Cite this article as: Papapetropoulos: NO-H₂S interactions involve cGMP. BMC Pharmacology and Toxicology 2013 14(Suppl 1):O32.

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