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Hydrogen Sulfide is an Inducer of Angiogenesis

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SUMMARY

Hydrogen sulphide (H_2S) is emerging as an important signalling molecule in the cardiovascular system. H_2S can be produced by endothelial cells and has been shown to relax vascular smooth muscle leading to reduced mean arterial blood pressure. H_2S is endogenously synthesized in a range of mammalian tissues through the activity of at least two enzymes, cystathionine β synthetase (CBS) and cystathionine γ lyase (CSE), the latter being mainly expressed in the vasculature. Herein, we studied the role of this gasotransmitter in angiogenesis.

In vitro, H_2S triggered endothelial cell (EC) growth and motility and induced the assembly of EC into tube-like networks. H_2S induced p38 MAPK phosphorylation; inhibition of p38 activity with SB203580 led to a reduction in the migratory rate of EC in response to H_2S. Activation of p38 and migration of cells treated with H_2S was inhibited by the ATP-sensitive (K^+_{ATP}) potassium channels channel blocker, glibenclamide. On the other hand, the K^+_{ATP} channel opener SG209 promoted EC migration. The results described above reveal the importance of K+ currents and MAPK pathways in the angiogenic actions of H_2S in vitro. To determine if H_2S also enhances angiogenesis in vivo we treated chicken chorioallantoic membranes (CAM) with H_2S; such treatment induced new vessel growth while topical administration of H_2S in a rat burn wound assay promoted re-epithilization and wound-healing.

To test whether endogenously produced H_2S affects angiogenesis, we used inhibitors of H_2S synthesis. Treatment of CAM with PAG or BCA reduced H_2S production and neovascularization, while exogenous addition of H_2S reversed the inhibitory actions of PAG or BCA in the CAM. To further investigate a possible role of endogenous H_2S to the actions of the well-known EC mitogen vascular endothelial growth factor (VEGF), we treated EC with VEGF. This induced H_2S release from EC, although concomitant application of H_2S and VEGF did not result in an additive effect in motility. Furthermore, pre-treatment of EC with PAG, BCA or K^+_{ATP} channel inhibitors reduced or even abolished VEGF-stimulated EC migration. siRNA knock-down of CSE attenuated VEGF-signalling and EC migration triggered by VEGF. In an aortic ring in vitro angiogenesis assay, addition of VEGF resulted in the growth of fewer vessels in rings from $CSE^{-/-}$ compared to wild-type rings. Moreover, in $CSE^{-/-}$ mice wound healing was delayed. Taken together the above mentioned results support a pro-angiogenic role for endogenous H_2S.

In conclusion, our findings indicate that H_2S enhances new blood vessel formation through a K^+_{ATP} channel/p38 pathway and that anti-diabetic agents that inhibit K^+_{ATP} channels may be useful tools in diseases where inhibition of neovascularization is desirable.