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Regulation of vascular growth and tone by hydrogen sulfide

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Hydrogen sulfide (H_2S) is a colourless, flammable gas with a characteristic pungent smell. Until recently, the H_2S literature was focused in the toxicology of this agent. Exposure to H_2S concentrations lower than 100 ppm lead to eye irritation, sore throat, dizziness, nausea, shortness of breath, and chest tightness, while exposure to 1000 ppm or more causes central nervous system toxicity and respiratory depression. In the past 5 years the interest for H_2S biology has seen an upsurge, as it was accepted that low amounts of this gas are endogenously produced in most mammalian tissues. Increasing evidence shows that H_2S acts as a signalling molecule in cells and is now considered the third member of the gasotransmitter family along with nitric oxide and carbon monoxide. Most of H_2S is produced by two enzymes cystathionine-synthase (CBS) and cystathionine γ-lyase (CSE) that use L-cysteine as a substrate and pyridoxal phosphate as a co-factor. CBS is highly expressed in the central nervous system, while CSE is abundantly present in the heart, lung, blood vessels, liver and kidney.

>In the cardiovascular system, H_2S has anti-apoptotic effects on cardiomyocytes, exerts cardioprotective actions and modifies vascular tone. We have recently shown that exogenously administered Na_2S stimulates endothelial proliferation, migration and capillary-like network formation. These effects of H_2S on migration are mediated through the activation of ATP-sensitive K^+-channels (K_{ATP}) and activation of mitogen activated protein kinase pathways. Inhibition of CSE and reduction of endogenously produced H_2S reduces vascular network length and branching of blood vessels in the chicken chorioallantoic membrane. Exposure of endothelial cells to vascular endothelial growth factor (VEGF) increased H_2S production and genetic or pharmacological inhibition of CSE restricted VEGF signalling and VEGF-driven angiogenic responses (migration, sprouting). Thus, H_2S is an endogenous activator of angiogenesis and modulation of its production might be useful in diseases characterized by aberrant or excessive angiogenesis.

H_2S exerts important biological actions in vascular smooth muscle cells. Originally H_2S–induced vasorelaxation was believed to be mediated by potassium channels (including K_{ATP} channels). However, significant vasodilation can be observed after sulfonylurea treatment, suggesting that additional pathways are involved. We recently showed that H_2S donors inhibit phosphodiesterase activity in vitro and that exposure to H_2S increases cGMP levels in smooth muscle cells. The cGMP elevating effects of H_2S are abolished following phosphodiesterase inhibition. Moreover, incubation of cells with H_2S led to an increase in VASP phopshorylation on Ser239, suggesting that H_2S activates PKG signalling pathways. More importantly, incubation of aortic rings with selective PKG-I inhibitors (DT-2, DT-3) attenuated H_2S-induced vasorelaxation. Our results reinforce the notion that H_2S plays important roles in vascular biology, by modulating vascular growth and tone.

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