Hydrogen sulfide regulates the redox status of soluble guanylate cyclase

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Soluble guanylate cyclase (sGC) is a 'receptor' for the endogenously produced gasotransmitter nitric oxide (NO). sGC exists as a heterodimer of an α and a β subunit, that carries a heme prosthetic group. Binding of NO to ferrous (Fe^{2+}) heme in the N-terminus of sGC β1 induces structural changes that are transmitted to the C-terminus of the protein increasing its catalytic activity and leading to the production of the second messenger cyclic guanosine-3',5'-monophosphate (cGMP) from guanosine 5`-triphosphate (GTP). About a decade ago, NO-independent activators and stimulators were discovered as promising agents for the treatment of cardiovascular and pulmonary diseases. These agents can activate sGC in a heme-dependent manner (sGC stimulators) or heme-independent manner (activators). Hydrogen sulfide (H_2S) is a new gasotransmitter with pleiotropic actions in mammalian cells. H_2S exerts both direct (ROS scavenging) and indirect (up-regulation of redox-sensitive genes and mechanisms) anti-oxidant actions.
In the present study we aimed to determine whether H_2S could regulate sGC redox state and affect its responsiveness to NO-releasing agents and sGC activators.
The ability of H_2S to alter responsiveness to a NO donor and BAY 58-2667 was tested using purified recombinant sGC, cultured rat aortic smooth muscle cells and pre-constricted mouse aortic rings in vitro.
Supplementation of ferric (Fe^{3+}) recombinant sGC with Na_2S led to heme reduction and to increased enzyme responsiveness to the NO donor sodium nitroprusside, while the same treatment caused a decrease in the responsiveness to BAY 58-2667. Using cultured cells, we observed that treatment with rotenone, that increases endogenous ROS production elevating ferric sGC, augmented cGMP accumulation in response to BAY58-2667; this effect was reversed by Na_2S. In contrast, treatment of cells with rotenone reduced DEANO-induced cGMP accumulation in a Na_2S-reversible manner.
In experiments with phenylephrine-constricted aortic rings, treatment with rotenone caused a rightward shift of DEANO concentration-response curve, an effect partially restored by incubation with Na_2S. When rings were pre-treated with Na_2S presumably leading to higher content of ferrous sGC heme, the concentration-response curve to BAY 58-2667 was shifted to the right.
These results suggest that H_2S can facilitate the reduction of sGC heme Fe from ferric to ferrous and maintain sGC in a NO-responsive state. This also limits the action of sGC to activators (BAY 58-2667). The described effect of H_2S on sGC provides an additional mechanism of cross-talk between the NO and H_2S pathways.