NO-mediated vascular smooth muscle relaxation in sGCα_1 knock-out mice

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Background

Nitric oxide (NO) is the active metabolite responsible for the relaxing influence of several endogenous and exogenous vasodilators. The predominant intracellular receptor for NO is soluble guanylyl cyclase (sGC), that consists of an α and a β subunit, each existing in 2 isoforms (α_1/α_2 and β_1/β_2). The $\alpha_1\beta_1$ isoform is most abundantly expressed and widely distributed. We investigated the functional importance of the α_1-subunit in vasorelaxations induced by endogenous NO and exogenous NO-donors.

Materials and Methods

Segments of the thoracic aorta and femoral artery from female and male homozygous sGC$\alpha_1^{-/-}$ mice and wild type littermates were mounted in a small vessel myograph for isometric tension recording. Concentration-response curves were established with acetylcholine (ACh) (1 nM – 10 μM), BAY 41-2272 (1 nM – 10 μM), sodium nitroprusside (SNP) (1 nM – 10 μM) and levcromakalim (Lev)(1 μM – 100 μM) in control conditions and/or in the presence of ODQ.

Results

The relaxing influences of both endogenous NO (released from the endothelium in response to ACh) and the exogenous NO-donor SNP were significantly decreased in the femoral artery and aorta from sGCα_1 knock-out mice. However, the impairment of the response to ACh was more pronounced than that of SNP. In the presence of the sGC-inhibitor ODQ, the difference in ACh- and SNP-induced response between the corresponding vessels from sGCα_1 knock-out- and wild type mice was significantly reduced. The response to the NO-independent sGC-activator BAY 41-2272 was also significantly diminished in blood vessels from sGCα_1 knock-out mice. Relaxations in response to the K_{ATP}-channel opener Lev were not different, indicating the specificity of the impairment of the sGC-related responses. All observations were similar in both sexes.

Conclusion

The results indicate the involvement an sGC isoform with the α_1 subunit in vascular relaxations induced by both endogenous and exogenous NO. However, the substantial relaxation remaining in sGCα_1 knock-out mice suggests the contribution of (an) additional pathway(s) in NO-induced relaxations. Also BAY 41-2272 exerts its effect at least in part through activation of an sGC isoform with the $\alpha_1$subunit.