NADPH oxidase 4 and endothelium-derived hyperpolarization factor play a role in maintaining vascular function in small resistance arteries

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Purpose: Endothelial dysfunction precedes the onset of cardiovascular and vascular complications. NADPH oxidase 4 (NOX4)-generated H_2O_2 might play a role in vasodilation of small resistance arteries in our mice models.
Methods: Vascular function of 2nd and 3rd branches of isolated mesenteric artery segments from 10-week-old wild-type (WT) and Nox4$^{-/-}$ mice was analysed using a wire myograph.
Results: Phenylephrine (PE)-induced contraction by calcium-release from intracellular compartments was similar in WT and Nox4$^{-/-}$ mice. Endothelium-dependent vasorelaxation induced by acetylcholine (Ach) was also similar in WT and Nox4$^{-/-}$ mice. However, application of catalase on vessel segments decreased ACh-induced vasorelaxation only in WT but not Nox4$^{-/-}$ mice. Blocking the large-conductance calcium-dependent potassium channels (BK channels) with paxilline induced endothelial dysfunction in WT mice but not Nox4$^{-/-}$ mice. In both WT and Nox4$^{-/-}$ mice cyclooxygenase-2 (COX-2) inhibitor diclofenac showed no change in endothelial function. The highest impact on endothelium-dependent vasorelaxation had NOS inhibitor N(ω)-Nitro-L-Arginine Methyl Ester (L-NAME). Incubation with L-NAME induced endothelial dysfunction in both mice strains. In addition, endothelial dysfunction could be further impaired by application of paxilline to L-NAME-blocked mesenteric segments of WT and Nox4$^{-/-}$ mice. Both WT mice and Nox4$^{-/-}$ mice showed significant endothelial dysfunction when blocked with paxilline and diclofenac. However, smooth muscle function was unchanged between groups.
Conclusion: In both WT and Nox4$^{-/-}$ mice, nitric oxide is the main vasodilator and can be regulated by endothelium-derived hyperpolarisation factors (EDHF). The presence of NOX4 in the mesenteric artery of WT mice mediates vasodilatory and compensatory mechanisms when normal physiological responses are inhibited.