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Review

Novel approaches to improving endothelium-dependent nitric oxide-mediated vasodilatation

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Abstract:
Endothelial dysfunction, which is defined by decreased endothelium-dependent vasodilatation, is associated with an increased number of cardiovascular events. Nitric oxide (NO) bioavailability is reduced by altered endothelial signal transduction or increased formation of radical oxygen species reacting with NO. Endothelial dysfunction is therapeutically reversible and physical exercise, calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor antagonists improve flow-evoked endothelium-dependent vasodilation in patients with hypertension and diabetes. We have investigated three different approaches, with the aim of correcting endothelial dysfunction in cardiovascular disease. Thus, (1) we evaluated the effect of a cell permeable superoxide dismutase mimetic, tempol, on endothelial dysfunction in small arteries exposed to high pressure, (2) investigated the endothelial signal transduction pathways involved in vasorelaxation and NO release induced by an olive oil component, oleanolic acid, and (3) investigated the role of calcium-activated K channels in the release of NO induced by receptor activation. Tempol increases endothelium-dependent vasodilatation in arteries from hypertensive animals most likely through the lowering of radical oxygen species, but other mechanisms also appear to contribute to the effect. While oleanolic acid leads to the release of NO by calcium-independent phosphorylation of endothelial NO synthase, endothelial calcium-activated K channels and an influx of calcium play an important role in G-protein coupled receptor-evoked release of NO. Thus, all three approaches increase bioavailability of NO in the vascular wall, but it remains to be addressed whether these actions have any direct benefit at a clinical level.

Key words: endothelium, nitric oxide, oleanolic acid, tempol, calcium-activated K channels