

Prof. Paul M.G. Vanhoutte is an experienced researcher with extensive publication on research on endothelial function in the cardiovascular system, and on drug design. While much research effort has been put on endothelium-derived relaxing factors, the role of endothelium-derived contracting factors (EDCF) has become the major focus of his research in the recent years.

Key Research Programme

Endothelial dysfunction is an early event for many vascular diseases. For example, endothelial dysfunction is manifested in both chronic hypertension, diabetes as well as in aging. As a result, not only are endothelial cells no longer able to secrete enough relaxing factors, there is also an increased release of endothelium-derived contracting factor (EDCF). In recent years, studies have confirmed that EDCF are prominent in arteries of spontaneously hypertensive rats and the production of EDCF requires an acutely augmented level of intracellular calcium, the activity of cyclooxygenase-1 and the activation of thromboxane-prostanoid (TP) receptors. The involvement of EDCF in the human hypertensive vasculature is illustrated by the observations that inhibitors of its production (cyclooxygenase inhibitors) as well as those of its action (TP receptor blockers) restore a near normal endothelial function.

Using Halpern-Mulvany wire myograph setup, endothelium-dependent increases in force that is sensitive to inhibition of cyclooxygenase is demonstrated in aged wild type C57BL/b6 mice (36-40 weeks old). The isoform of cyclooxygenase that is responsible for the production of EDCF in these old mice is cyclooxygenase-1, as endothelium-dependent contractions is present in the aorta of COX2^{-/-} knockout mice, but not COX1^{-/-} knockout mice. The release of EDCF is regulated by nitric oxide, an endothelial-derived relaxing factor, such that a reduction in the release or bioavailability of nitric oxide augments the amplitude of the endothelium-dependent contractions. This phenomenon is observed not only in old rats but also in spontaneous hypertensive rats and streptozotocin-induced type I diabetic rats. In addition, previous exposure to acetylcholine (an endothelium-dependent relaxing agent) and sodium nitroprusside (a nitric oxide donor) exert delayed inhibition of EDCF-mediated contractions. While this effect of sodium nitroprusside is downstream of the calcium rise and is mainly nitric oxide-dependent, that of acetylcholine is nitric oxide-independent and upstream of the increase in calcium concentration that triggers the release of EDCF.

Representative Publications

Tang EHC, Feletou M, Huang Y, Man RYK, Vanhoutte PM. Acetylcholine and sodium nitroprusside cause long-term inhibition of EDCF-mediated contractions. *Am J Physiol Heart Circ Physiol* 2005; 289: H2434-H2440.

Tang EHC, Ku DD, Tipoe GL, Feletou M, Man RYK, Vanhoutte PM. Endothelium-dependent contractions occur in the aorta of wild-type and COX2^{-/-} knockout but not COX1^{-/-} knockout mice. *J Cardiovas Pharmacol* 2005; 46: 761-765.

Shi Y, Ku DD, Man RYK, Vanhoutte PM. Augmented EDHF-mediated relaxations attenuate endothelial dysfunction in femoral and mesenteric, but not in carotid arteries from type I diabetic rats. *J Pharmacol Exp Ther* 2006; in press.