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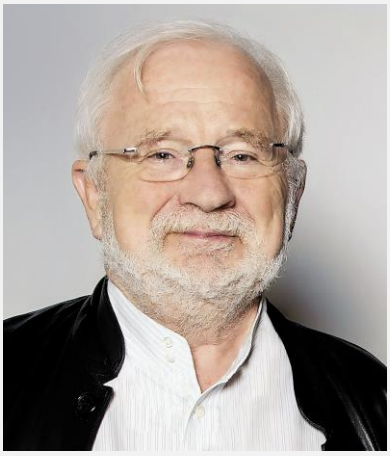
Thirty years of NO research: from good to bad…



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In the last thirty years, it became overwhelmingly apparent that the endothelium releases relaxing factors (EDRF), which diffuse to the underlying vascular smooth muscle cells and elicit endothelium-dependent vasodilatations. The best characterized EDRF is nitric oxide (NO) formed by endothelial NO synthase (eNOS). In the vascular smooth muscle cells, NO stimulates soluble guanylate cyclase which normally produces cyclic GMP. NO release by eNOS can be augmented by increases in shear stress or by activation of endothelial cell membrane receptors (e.g. in response to α2-adrenergic agonists, serotonin, vasopressin, adenosine diphosphate and bradykinin). The ability of the endothelial cell to release NO can be up-regulated by estrogens, repeated increases in blood flow, exercise, diet (ω3-unsaturated fatty acids, polyphenols), and down-regulated by oxidative stress and increased presence of oxidized low density lipoproteins (LDL). The bioavailability of NO is curtailed by aging, smoking, environmental pollution or obesity and in hypertension and diabetes. In addition to lesser direct relaxation of the underlying vascular smooth muscle, a decreased release of NO also permits the production of vasoconstrictor prostanoids and/or endothelin-1. Blunted endothelium-dependent relaxations can also be due to unresponsiveness of the vascular smooth muscle to NO. Finally, in coronary arteries, hypoxia causes acute augmentations of vasoconstrictor responses that depend on the presence of NO and the biased activation of soluble guanylate cyclase which produces cyclic IMP rather than cyclic GMP. Since hypoxia is implicated in exaggerated vasoconstrictions observed in coronary artery disease, the emerging role of this non-canonical cyclic nucleotide may help identifying novel therapeutic targets.

Biographical Sketch

Dr Paul M. Vanhoutte obtained his M.D. degree at the University of Gent (Belgium). He has been Professor of Pharmacology at the University of Antwerp, the Mayo Clinic (Rochester MN) and Baylor College of Medicine (Houston TX,). From 1992 to 2002, he was Director of Discovery Research at Servier (France). Since 2003 he is Professor in the Department of Pharmacology and Pharmacy of the Li Ka Shing Faculty of Medicine of the University of Hong Kong. Dr Vanhoutte is Doctor honoris causa of the Universities of Gent, Antwerp, Zürich, Montréal and Strasbourg, of RMIT and Monash Universities in Melbourne, and of the Gr. T. Popa University in Romania. Dr. Vanhoutte is a Highly Cited Researcher (ISI) in three categories: Biology & Chemistry, Pharmacology, and Clinical Medicine. His current h-index is 125. His major scientific contribution has been to appreciate and analyse the importance of endothelial cells in the control of the underlying vascular smooth muscle in health and disease, and to highlight the complexity of that regulation.

Key references:

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