Quick Change Artist
Endothelium-Derived Relaxing Factor in Resistance Arteries

William F. Jackson

See related article, pp 802–808

vascular endothelial cells importantly contribute to the regulation of vascular smooth muscle tone through the production of a variety of vasoactive substances and by direct electric communication through myoendothelial gap junctions.\cite{1,2} Moncada et al\cite{3} discovered the first endothelium-derived vasoactive substance, prostacyclin, in the mid 1970s and rapidly identified its structure and chemical composition.\cite{3} This was followed by the landmark observations of Furchgott and Zawadzki.\cite{5} and the discovery of endothelium-derived relaxing factor in 1980. Seven years later, the endothelium-derived relaxing factor of Furchgott and Zawadzki was positively identified as NO.\cite{6} The existence of a nonprostaglandin, non-NO endothelium-derived hyperpolarizing factor (EDHF) was postulated by Komori et al\cite{7} in 1988. Twenty-three years later, we know that there is no one EDHF, but rather multiple pathways by which endothelial cells can produce hyperpolarization-induced relaxation of overlying vascular smooth muscle cells, independent from prostacyclin and NO (Figure).\cite{1,2}

The study by Boettcher and de Wit\cite{8} in this issue of Hypertension supports this hypothesis by demonstrating that the phenotype of nonprostaglandin-, non–NO-mediated, acetylcholine (ACh)-induced vasodilatation can be modulated by the preparation used to study the phenomenon. These authors show that, whereas ACh-induced relaxation of vessels studied in a wire myograph under isometric conditions is highly dependent on endothelial cell expression of connexin 40, ACh-induced vasodilatation of the same vessels studied under isobaric conditions in a pressure myograph, or studied in vivo, appears independent from connexin 40 expression.

The implications of this study are ±2-fold. First, as the authors point out, one must take care in extrapolating results from in vitro experiments to regulation of vascular tone, in vivo. Second, and more interestingly, the authors’ findings suggest that the mechanisms underlying nonprostaglandin, non-NO–mediated endothelium-dependent (EDHF-like) vasodilatation can rapidly change depending on the circumstances in the same blood vessel. This implies that the pathways involved are mutable not only by the experimental conditions but possibly by the physiological or pathophysiological status of the system. The authors’ findings add to our understanding of endothelial cell function in health and disease.\cite{1,2}

The study by Boettcher and de Wit\cite{8} also leaves a number of questions unanswered. First, the identity of the EDHF, or the EDHF-like pathway that is responsible for the ACh-induced smooth muscle relaxation observed in the pressure-myograph, and also in vivo, remains to be established. The lack of effect of connexin 40 deletion on ACh-induced vasodilatation under isobaric conditions indicates that direct electric communication from endothelial cells to smooth muscle cells, via connexin 40–based gap junctions, is not involved under isobaric conditions in vitro or in vivo. Previously\cite{9} it was shown that ACh-induced dilatation of pressurized mouse gracilis arteries is mediated by release of K+ ions through endothelial Ca2+-activated K+ channels and subsequent activation of smooth muscle inward rectifier K+ channels and the Na+/K+ ATPase (see left side of Figure). This mechanism would not require myoendothelial gap junction communication to produce ACh-induced vasodilatation of these murine blood vessels under isobaric conditions. However, in pressurized rat gracilis arteries studied in vitro, cell-cell communication via gap junctions appears requisite for ACh-induced vasodilatation.\cite{10} This either means that there are substantial species-dependent differences in mechanisms (which is clearly possible\cite{3}) or that the EDHF-like mechanisms in gracilis arteries are more complicated than previously assumed. It is worthy to note that neither the study by Boettcher and de Wit\cite{8} nor that by Krummen et al\cite{9} excludes gap junction-based mechanisms involving connexins other than connexin 40 in the murine gracilis artery.

Second, the mechanisms responsible for the switch of the phenotype of the EDHF-like responses have yet to be identified. Boettcher and de Wit\cite{8} suggest that it may be related to differences in wall tension between the isometric and isobaric conditions. However, this hypothesis was not tested, and the signaling pathways involved were not provided. Previous studies in rat mesenteric resistance arteries suggest that the mechanism of ACh-induced, EDHF-like dilation depends on the level of vasoconstrictor-induced tone: at high levels of agonist-induced tone, connexin 40–based mechanisms dominate, whereas at more moderate levels of tone, EDHF-like dilation appears independent from connexin 40–based mechanisms.\cite{11} Boettcher and de Wit\cite{8} used similar concentrations of norepinephrine to constrict mouse gracilis arteries in both the wire-myograph (isometric) and pressure-myograph (isobaric) preparations in an attempt to produce similar levels of smooth muscle activation. However, the
authors did not verify that the concentration of vasoconstrictor agonist used was equi-effective in the 2 preparations. Direct comparison of norepinephrine concentration-response relationships between vessels studied in a wire myograph (isometric) and a pressure myograph (isobaric) have shown that norepinephrine is actually more potent in the isobaric (isometric) and a pressure myograph (isobaric) have shown that norepinephrine is actually more potent in the isobaric preparation. This is the opposite of what would be required to produce a “switch” in EDHF-like mechanisms as proposed by Mather et al.11

Figure. Pathways for nonprostacyclin-, non-NO–mediated, endothelium-dependent hyperpolarization of vascular smooth muscle in resistance arteries. Schematic diagram of a longitudinal section through a resistance artery showing smooth muscle and endothelial cell cross-sections and depicting several potential pathways by which ACh can produce endothelium-dependent smooth cell hyperpolarization and vasodilatation independent from prostaglandins and NO. On the left, ACh-induced increases in intracellular Ca2+ activate endothelial small conductance (sKCa) and intermediate conductance (IKCa) Ca2+-activated K+ channels. The released K+ ions can then act as an EDHF through activation of smooth muscle inward rectifier K+ channels (Kir) or Na+/K+ ATPase. Smooth muscle hyperpolarization then closes voltage-gated Ca2+ channels (VGCC), leading to a fall in smooth muscle Ca2+ and vasodilatation. Alternatively, as shown in the center of the diagram, endothelial cell hyperpolarization produced by activation of sKCa or IKCa channels, as described above, can be directly transmitted to smooth muscle cells via myoendothelial gap junctions to produce vasodilatation. As shown in the right side of the diagram, the increase in endothelial cell Ca2+ produced by ACh can also lead to the synthesis of factors such as epoxydides (epoxyeicosatrienoic acids; EETs) of arachidonic acid (AA) produced by cytochromes P450 (CYP) or lipoxigenase (LOX) products such as trihydroxyeicosatrienoic acid (THETA). EETs may activate transient receptor potential V4 (TRPV4) channels on smooth muscle cells leading to Ca2+ influx, which then triggers Ca2+ release from smooth muscle stores through ryanodine receptors (RyR) in the form of Ca2+ sparks, which, in turn, activate smooth muscle large conductance Ca2+-activated K+ channels (BKCa). This leads to smooth muscle hyperpolarization and vasodilatation as outlined above. THETA may directly activate BKCa channels to produce smooth muscle hyperpolarization and vasodilatation. Additional pathways also are possible; see References 1 and 2 for additional information. PLA2 indicates phospholipase A2; PLCβ, phospholipase Cβ; IP3, inositol 1,4,5-trisphosphate; SERCA, smooth endoplasmic reticulum Ca2+ ATPase.

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References

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