Endothelium-Derived Relaxing Factor in Resistance Arteries

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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.1,2 Moncada et al3 discovered the first endothelium-derived vasoactive substance, prostacyclin, in the mid 1970s and rapidly identified its structure and chemical composition. This was followed by the landmark observations of Furchgott and Zawadzki,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.6 The existence of a nonprostaglandin, non-NO endothelium-derived hyperpolarizing factor (EDHF) was postulated by Komori et al7 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).1,2

The study by Boettcher and de Wit8 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.1,2

The study by Boettcher and de Wit8 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, 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.9 This either means that there are substantial species-dependent differences in mechanisms (which is clearly possible) 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 Wit8 nor that by Krummen et al9 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 Wit8 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 dilatation appears independent from connexin 40–based mechanisms.10 Boettcher and de Wit8 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 was reported in Boettcher and de Wit9 and particularly to define their role in pathologies that affect vascular function. Obviously, additional experiments will be required to determine what is responsible for the differences reported by Boettcher and de Wit9 and particularly to define their role in pathologies that affect vascular function. Ideally these experiments should include simultaneous measurement of smooth muscle and endothelial cell membrane potential, more direct assessment of gap junction-based communication (eg, using current injection), and precise quantitation of the level of agonist-induced smooth muscle activation in the 2 experimental preparations. More attention to the study of EDHF mechanisms in vivo would also appear warranted. It also remains to be established whether changes in wall tension, as could be produced by changes in luminal pressure alone, in the absence of added vasoconstrictors, can modulate the mechanisms underlying EDHF-like responses in resistance arteries and arterioles that develop substantial myogenic tone. Better understanding of these pathways may help to clarify changes in vascular function that produce or are affected by diseases like hypertension. These mechanisms also may provide new targets for the development of therapies to treat and potentially prevent hypertension or other pathologies that affect vascular function.

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References


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