EDHF and NO
Different Pathways for Production—Similar Actions

William M. Chilian, Ryoji Koshida

The observation that Hsp90 is required for endothelial NO synthase (eNOS) function is well documented by several laboratories.3,4 The present observations confirm these reports.1 The novel aspect of these particular findings is that Hsp90 is not required for the synthesis and/or actions of EDHF.

Véquaud and Thorin1 also reported that EDHF is not a metabolite of phospholipase C and does not require increases in intracellular calcium for production. Although these data do not reveal the identity of EDHF in the mesenteric artery, they suggest what it is not. Along this line, it is worth mentioning that the identity of EDHF is controversial, and our opinion for the basis of this controversy relates to the likelihood that there are many EDHFs. Some groups report that EDHF in coronary arteries and arterioles is a lipid metabolite of cytochrome P450.5–7 and the general presumption is that the lipid substrate for cytochrome P450 is produced by the actions of phospholipase C on membrane phospholipids. However, several other groups have reported that EDHF is not a metabolite of cytochrome P450, and the identity has been suggested as enandimides, K+-, or other fatty acid metabolites.8–11 The authors also observed that Ca2+ signaling is not involved in the production of EDHF, which contrasts greatly to the signal cascade activated during agonist-induced production of NO. Despite their compelling results, a caveat should be mentioned: with the probable existence of many EDHFs, one should not necessarily conclude that Ca2+ is not involved, because in another EDHF, this cation may hold a seminal role.

An important aspect of the results presented by Véquaud and Thorin1 relates to the differential G protein signaling involved in the production of NO and EDHF. In a similar vein, one should also exercise caution regarding a general conclusion about the involvement of G proteins in all EDHFs. Because of the many organ system and species differences that seem to underscore the many faces of EDHF, a universal involvement of a certain G protein in the production of this vasodilator seems unlikely. Despite this caveat, the authors’ results that G protein α-subunits and β-subunits are involved in NO- and EDHF-mediated vasodilation, respectively, are important. This conclusion, and advance, was revealed by administration of the specific antibody against the particular G-protein subunit to the endothelium of the intact vessel. Because the antibody was administered intraluminally, the effect is largely confined to endothelial cells. This is important to highlight because it engendered the authors to discriminate between the production of the vasodilator versus the actions of the substance. The results also imply a level of discrete regulation of the production of EDHF and NO. Moreover, the existence of discrete signaling pathways to
produce vasodilation may be underscored by a necessity to evolve parallel or redundant controls. Such a system would have the safeguards of backup controls, which may be important in the event one of the dilator pathways is compromised.

In the aggregate, the observations that EDHF is distinct from NO would appear to confer some benefits to vascular control mechanisms. Sir Isaac Newton once stated, “Nature does not believe in the pomp of superfluous causes,” which in the context of the cardiovascular system implies that systems exist because they offer an advantage in the regulation of blood flow and vasomotor tone. Having both NO and EDHF as regulatory systems is most likely important. If one particular system fails, then the parallel or backup system could be activated to assume vasomotor control. Such interactions between NO and EDHF have been observed previously. As the report by Véquaud and Thorin demonstrates, EDHF and NO produce a similar net effect, ie, vasodilation, but are distinct insofar as they are produced by completely different signaling cascades. This scheme for vasomotor control would appear advantageous, because parallel or backup controls would be produced by different transduction pathways and would likely have different downstream biochemical effectors. Thus, the coexistence of distinctive transduction pathways for the production of NO and EDHF would appear to confer flexibility and safeguards in the control of organ blood flow under a variety of physiological and pathophysiological conditions.

References

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