Standing out in a crowd: knockout of ApoE increases the potency of endothelium-dependent vasodilators in mesenteric arteries

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This editorial refers to ‘Enhanced K+ -channel-mediated endothelium-dependent local and conducted dilation of small mesenteric arteries from ApoE−/− mice’ by T. Beleznai et al., pp. 199–208, this issue.

Hypercholesterolaemia is a risk factor for cardiovascular disease, and a number of prior studies have shown that endothelium-dependent vasodilation is compromised in animal models of this condition1–4 as well as in humans.5–7 The study by Beleznai et al.8 goes against this trend and demonstrates that small mesenteric arteries from apo-lipoprotein E-knockout (ApoE−/−) mice are actually more sensitive to endothelium-dependent vasodilators than are vessels from wild-type mice. Increased vasodilator potency has been previously reported in other models of dyslipidaemia, but only after inhibition of NO and prostaglandin synthesis.9–11 These studies clearly demonstrate that there is significant regional heterogeneity in the vascular adaptation to loss of ApoE, which has implications for the design and application of drugs and therapies directed at combating the vascular consequences of hypercholesterolaemia. What remains to be established are the mechanisms responsible for the increased potency of endothelium-dependent vasodilators in small mesenteric arteries of ApoE−/− mice (and in hypercholesterolaemia, in general), as well as the physiological (or pathophysiological) significance of this change in vascular reactivity.

Beleznai et al.8 show that the leftward shift of the concentration–response relationship for a protease-activated receptor-2 (PAR-2) agonist, observed in mesenteric arteries from ApoE−/− mice during pressure myography, is conserved as an increase in the sensitivity of agonist-induced changes in endothelial cell [Ca2+]i. These data suggest that at least part of the increase in endothelium-dependent vasodilator potency occurs at the level of, or upstream from, endothelial cell Ca2+ release and influx events, and could be related to changes in receptor density or the efficiency of coupling between PAR-2 and downstream Ca2+ signalling.8 Hypercholesterolaemia has been shown to modulate the expression and function of many ion channels involved in vascular reactivity.9,10 Thus, it is also possible, and highly likely that the hypercholesterolaemia that results from knockout of ApoE alters the function of ion channels responsible not only for agonist-induced increases in endothelial cell [Ca2+]i, but also for transduction of this Ca2+ signal into changes in membrane potential, transmission of changes in membrane potential within and along the vessel wall, and transduction of changes in vascular smooth muscle membrane potential into smooth muscle relaxation. Consistent with this hypothesis, Beleznai et al.8 pharmacologically demonstrated that there was a switch in the role played by various Ca2+-activated K+ channels in vasodilation induced by PAR-2 activation in arteries from ApoE−/− mice. Unfortunately, membrane potential was not measured in the vessels from the knockout mice, such that the relationship between endothelial cell Ca2+ signals and changes in endothelial cell and smooth muscle cell membrane potential after loss of ApoE expression remains unknown.

Despite the increase in sensitivity to both acetylcholine and a PAR-2 agonist, Beleznai et al.8 found that conduction of vasodilation along small mesenteric arteries was unchanged in vessels from ApoE−/− mice. These data support findings from an in vivo study in cremaster muscles that also found no difference in conduction of vasodilation induced by acetylcholine between wild-type and ApoE−/− mice.1 However, in the cremaster arterioles, the potency of acetylcholine to induce dilation was substantially decreased.11 Thus, it appears that regardless of the status of endothelium-dependent reactivity, conduction of vasodilator signals along blood vessels is preserved in at least one model of hypercholesterolaemia. The physiological significance of this finding was not established in these studies, but it may mean that conducted vasomotor events are crucial to homeostasis and that the system has evolved to preserve this aspect of vascular reactivity in health and disease.

Similarly, the significance of conducted vasomotor events that arise from blood-borne signals in arteries, such as those likely to activate endothelial cell PAR-2, is not clear. Although it is evident that dilation originating in the microcirculation and ascending out of an organ or tissue into upstream resistance arteries is essential to deliver sufficient blood flow to active tissues,13 conducted dilation elicited by a blood-borne agonist would, presumably, precede the flow of blood. Conducted vascular responses are transmitted very quickly as they are mediated by electrical events,14 thus, changes in vessel diameter

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downstream would likely precede arrival of the blood-borne agonist, providing a feed-forward, anticipatory reaction. Further research will be required to establish the significance of such a mechanism in the regulation of blood flow to tissues as well as in the regulation of blood pressure in health and disease.

Finally, as noted above, the studies by Beleznai et al.⁸ support the hypothesis that there are substantial regional differences in the effects of hypercholesterolaemia (or more correctly, knockout of ApoE) on endothelium-dependent reactivity. For example, in coronary arteries, the efficacy of acetylcholine to produce dilation was substantially reduced in vessels from ApoE⁻/⁻ mice.³ In contrast, only mild attenuation was observed in gracilis arteries from these knockouts.⁴ In turn, these results differ from findings in cremaster arteries in vivo¹ and those of Beleznai et al.⁸ in mesenteric arteries in vitro where the efficacy of acetylcholine was unchanged. However, as noted above, in contrast to the increase in the sensitivity of mesenteric arteries to endothelium-dependent agonists observed by Beleznai et al.⁸ studies in cremaster muscle arteries demonstrated a decrease in sensitivity to acetylcholine.¹ Although differences in methods and experimental conditions cannot be ruled out as a cause of the dissimilarities in endothelium-dependent reactivity among the vessels studied, these findings suggest that there is substantial regional heterogeneity in the adaptation of arteries to knockout of ApoE. Identification of the proteins and signalling pathways responsible for such regional differences in blood vessels could provide new targets for the development of organ- or tissue-specific drugs or therapies to prevent or treat the vascular consequences of hypercholesterolaemia and other diseases or pathologies.

Conflict of interest: none declared.

Funding
Supported by Public Health Service Grants RO1 HL086483 and PO1 HL070687.

References