Role of 20-HETE in the Modulation of Myogenic Reactivity

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B. aylii sl first suggested that distention (stretch) of the wall, elicited by increases in intravascular pressure, acts as a facilitating stimulus on the vascular smooth muscle (VSM) to intensify its activity, eliciting constriction of blood vessels. Since this original hypothesis was offered, it has been recognized that this pressure-sensitive response, a contriction to elevation and a dilation to reduction of transmural pressure, originates from the smooth muscle layer of blood vessels and is independent of neural, hormonal, and metabolic influences. Although it is most pronounced in arterioles, it can also be demonstrated frequently in all types of blood vessels and lymphatics. The myogenic response contributes to autoregulation of blood flow and is believed to be one of the primary mechanisms responsible for the basal tone of small blood vessels. Consequently, it also influences capillary hydrostatic pressure.

Although there is no general agreement as to the nature of the transduction mechanisms mediating the myogenic response, there is a consensus that stretch of the VSM membrane results in membrane depolarization, leading to augmented Ca$^{2+}$ influx through increased voltage-gated Ca$^{2+}$ channel activity and contraction of VSM via Ca$^{2+}$-calmodulin–induced myosin light chain kinase phosphorylation. Among the mediators that have been proposed to be involved in the mechanotransduction of the stretch signal are activation of phospholipase C and A2, the adenylate cyclase/cAMP/protein kinase A signaling pathway, protein kinase C– and tyrosine kinase–mediated mechanisms, and a variety of ion channels, as well as integrins and elements of the cytoskeleton of VSM.

In this issue of Circulation Research, Gebremedhin et al expand on their previous findings and confirm the participation of 20-HETE in the myogenic control of rat cerebral arterioles. By a variety of methods, they demonstrate that cerebral arterial VSM cells express P450 4A mRNA and proteins that catalyze the synthesis of 20-HETE via ω-hydroxylation of arachidonic acid. In addition, they show a 6-fold increase in the concentration of 20-HETE (as measured by gas chromatography–mass spectrometry) in rat cerebral artery segments in response to an increase in transmural pressure from 20 to 140 mm Hg. The vasoconstrictive effects of 20-HETE were blocked by the 20-HETE antagonists 15-HETE and 20-HETE. Coupled with the findings that renal and cerebral arterioles produce 20-HETE, which is the primary product in renal microvessels and exceeds the formation of cyclooxygenase and lipoxygenase products, the results of Gebremedhin et al argue in favor of the notion that this compound may serve as an autocrine factor, regulating vascular tone. Lending additional support to this notion are results of experiments showing that 20-HETE augments inward Ca$^{2+}$ currents in cerebral VSM and its inhibitors block pressure-induced myogenic tone in renal arterioles. Of particular interest is that, according to the authors, nitric oxide (NO) modulates 20-HETE formation by binding to the heme moiety of P450 4A enzymes and inhibits the formation of 20-HETE. Moreover, they also have shown that in renal arterioles, inhibition of 20-HETE synthesis could contribute to the cGMP-independent vasoconstrictor effect of NO via the direct activation of large-conductance K_Ca channels.

In the present study, Gebremedhin et al expand on their previous findings and confirm the participation of 20-HETE in the myogenic control of rat cerebral arterioles. By a variety of methods, they demonstrate that cerebral arterial VSM cells express P450 4A mRNA and proteins that catalyze the synthesis of 20-HETE via ω-hydroxylation of arachidonic acid. In addition, they show a 6-fold increase in the concentration of 20-HETE (as measured by gas chromatography–mass spectrometry) in rat cerebral artery segments in response to an increase in transmural pressure from 20 to 140 mm Hg. The vasoconstrictive effects of 20-HETE were blocked by the 20-HETE antagonists 15-HETE and 20-HETE. Of particular interest is that, according to the authors, nitric oxide (NO) modulates 20-HETE formation by binding to the heme moiety of P450 4A enzymes and inhibits the formation of 20-HETE. Moreover, they also have shown that in renal arterioles, inhibition of 20-HETE synthesis could contribute to the cGMP-independent vasodilator effect of NO via the direct activation of large-conductance K_Ca channels.

These are indeed exciting findings, and they underscore and substantiate the notion that 20-HETE is an endogenous regulator of vascular reactivity in the microcirculation. That 20-HETE synthesis occurs primarily in small, myogenically active resistance vessels rather than larger, myogenically inactive conduit type vessels also argues in favor of its putative role in the control of vascular tone. Nevertheless, the authors’ thesis that 20-HETE has a major role in the auto-
regulation of cerebral blood flow is not yet proven definitively and requires the additional demonstration of this mediator’s ability to inhibit myogenic dilation in response to a lowering of transmural pressure. In a previously published study, the authors reported that in both renal and cremaster muscle arterioles of rats, the P450 4A enzyme family is likely to function as an oxygen sensor and control arteriolar diameter by generating 20-HETE in an oxygen-dependent manner. Because 95% O₂ was used to suffuse the vessels in the present study of isolated cerebral arteries, it is of concern that, under these conditions, the high baseline release of 20-HETE may have increased arteriolar tone, consequently favoring enhanced myogenic reactivity and its attenuation by DDMS. Furthermore, to be absolutely certain of the role of 20-HETE in the generation of myogenic tone, additional experiments investigating the possible effects of DDMS and the antagonists of 20-HETE on Ca²⁺ channels would have to be performed since the results in the present study conceivably could be explained on the basis of their ability to directly inhibit Ca²⁺ channels. Because pressure acts through membrane depolarization, what is still to be tested is whether the inhibitors selectively inhibit pressure-induced depolarization. If, indeed, 20-HETE acts solely through the inhibition of large-conductance Kᵥ channels, then one would also expect that inhibition of these channels by tetraethylammonium or iberiotoxin would eradicate the effects of DDMS on arteriolar diameter as well as cerebral blood flow regulation. Experiments of this type would certainly lend additional support to the authors’ hypothesis.

Many aspects of delineating the mechanisms of action of 20-HETE remain to be addressed. On the basis of the studies reported, 20-HETE inhibits only a portion, albeit a significant one, of the myogenic response in renal and cerebral arterioles. It would be fascinating to learn what other agents and signaling molecules are responsible for the full expression of myogenic reactivity and possibly autoregulation of blood flow. Another intriguing question that needs to be answered is whether 20-HETE has a role in the regulation of vascular tone in tissues other than those already reported, such as the skeletal muscle and coronary circulation of experimental animals, as well as humans. Regardless of the outcome of these studies, the authors provided overwhelming evidence of the importance of 20-HETE in the regulation of microvascular function. This evidence is consistent with their provocative hypothesis, and it merits continued consideration.

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References


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