Vascular pathologies associated with the heart, brain, and peripheral blood vessels remain the leading cause of death in the Western world, accounting for over 960,000 deaths in 1999 in the United States alone. One of the difficulties in elucidating the mechanisms contributing to vessel disease has been in fully understanding how the vascular system maintains basal vascular tone and autoregulates blood flow and capillary hydrostatic pressure. It is now known that one of the processes participating in these vital functions is the myogenic response.

The myogenic response, first defined by Bayliss in 1902, describes the response of arterial blood vessels to changes in luminal pressure. Typically, it involves constriction of the vessel in response to increases in transmural pressure and dilation in response to pressure reduction. It is most pronounced in resistance vessels and arterioles. The myogenic response participates in local regulation of blood flow and protects from large changes in pressure induced by postural changes.

Recently, interest has focused on the integrin family of adhesion molecules as possible “transducers” of changes in vascular smooth muscle tension. The integrins are a large family of cell-cell adhesion receptors comprising at least 16 α and 8 β subunits that can heterodimerize to produce more than 20 transmembrane receptors. The integrins can recognize ligands of the extracellular matrix and transmit extracellular stimuli into intracellular signaling events because they are located amongst a network of extracellular matrix proteins including several types of collagen, laminin, elastin, fibronectin, vitronectin, and osteopontin. Association of integrins with extracellular matrix proteins and cytoskeletal proteins induces clustering to the focal adhesion or dense body. Contractile proteins attach to the plasma membrane at this site and phosphorylation of nonreceptor tyrosine kinases and focal adhesion kinases occur here. As a result of their close association with the cytoskeleton and the extracellular matrix, integrins have been implicated as possible sensors in the myogenic response. However, no evidence to date is able to specifically link integrin signaling with the myogenic response.

Role of Integrins in the Control of Vascular Tone

Much of the evidence to support a possible role for integrins in the myogenic response comes from studies demonstrating that peptides containing integrin-specific amino acid sequences are vasoactive. The Asp-Gly-Asp (RGD) sequence is found in at least 4 integrins expressed in vascular smooth muscle and in wall proteins such as collagen and fibronectin. The RGD-containing peptides bind the integrins that contain the sequence and prevent cell adhesion to substrates such as collagen that also contain the sequence. Studies using the RGD peptides have reported arteriolar vasodilation (suggesting an inhibition of the myogenic response) and constriction of renal arterioles. This is because different integrins appear to mediate specific vasomotor responses. Although the mechanisms involved in the vasoconstrictions produced by the peptides are not clear, these studies support a role for the RGD sequence-containing integrins in the control of vasomotor tone.

Role of Calcium in the Control of Vasomotor Tone Versus Myogenic Tone

Additional support for a role for integrins in the myogenic response lies in the common role of Ca\(^{2+}\) in integrin signaling and in the maintenance of myogenic tone. It is well established that Ca\(^{2+}\) is central to smooth muscle contraction and establishing tone in single arterioles. Myogenic tone is dependent on influx of Ca\(^{2+}\) through L-type Ca\(^{2+}\) channels because dihydropyridines inhibit the myogenic response. However, little data supports a dependency on the release of intracellular Ca\(^{2+}\) (for review see Davis and Hill). It appears that the release of calcium is more likely to play a regulatory role in myogenic contraction. It is also not clear whether myogenic activation is associated with an increase in Ca\(^{2+}\) sensitization.

Integrins can enhance or decrease Ca\(^{2+}\) influx through L-type Ca\(^{2+}\) channels. This provides evidence that the extracellular matrix can exert control over L-type Ca\(^{2+}\) channel function through integrins. However, because integrins can initiate changes in intracellular Ca\(^{2+}\) levels, it has yet to be determined whether the effects of integrins on intracellular Ca\(^{2+}\) handling are consistent with those occurring during a myogenic contraction.

Common Signaling Pathways

Additional support for the role of integrins in the myogenic response lies in the signaling pathways activated. Increases in tyrosine phosphorylation and mitogen-activated protein (MAP) kinase activity have been demonstrated in cells subjected to stretch and shear stress. Consistent with a role in mechanotransduction, integrin binding at the extracellular matrix activates MAP kinases.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Physiology, The University of Western Australia, Crawley, Western Australia.

Correspondence to Dr Livia C. Hool, Dept of Physiology, The University of Western Australia, Stirling Highway, Crawley, WA, 6009, Australia. E-mail lhool@cyllene.uwa.edu.au

(Circ Res. 2002;90:371-373.)

© 2002 American Heart Association, Inc.

Circulation Research is available at http://www.circresaha.org

DOI: 10.1161/01.RES.0000012916.66975.26

371
Activators of protein kinase C (PKC) are potent vasoconstrictors and studies indicating that norepinephrine enhances myogenic responsiveness implicate PKC as a mediator. Smooth muscle stretch and increased intraluminal pressure has been shown to activate phospholipase C (PLC) and increase inositol 1,4,5-trisphosphate (IP_3) content. However, the mechanisms by which PLC and other membrane-bound phospholipases are activated during myogenic contractions are unknown.

Although significant advances in the understanding of the mechanisms underlying the myogenic response have been made, it is clear that many areas have yet to be resolved. In this issue of Circulation Research, Waikutus-Edwards et al provide some additional insight into this complex area. In a series of studies examining the role of integrins in the control of vasomotor tone, they identify a role for the αβ₁ integrin. Using novel peptides that contain the Leu-Asp-Val (LDV) sequence, they are able to elicit concentration-dependent constriction in rat skeletal muscle arterioles. The LDV sequence is found in the CS-1 region of an alternatively spliced fibronectin variant. As a result of interaction between the αβ₁ integrin and the peptides, L-type Ca²⁺ channel current was enhanced and intracellular Ca²⁺ was increased. The constriction could be abolished with the anti-β₁ integrin antibody and the L-type Ca²⁺ channel inhibitor nifedipine and was unaffected by removal of the endothelium. The authors also provide some insight into the mechanism, establishing that the vasoconstrictor response could be abolished with the Src-family kinase inhibitor PP2. This is consistent with signaling linking αβ₁-integrin activation of L-type Ca²⁺ channels and with other studies implicating the possible involvement of Src-family kinases in myogenic responses.

It is not established whether the effects are due to a direct phosphorylation of the channel by a nonreceptor tyrosine kinase or whether activation of the channel involves additional intermediates. The authors also find that inhibition of PKC was unable to alter the vasoconstriction induced by the peptides but could attenuate the basal vascular tone. This suggests that PKC is not involved in the regulation of the channel by the αβ₁ integrin.

The results by Waitkus-Edwards et al provide support for the involvement of an axis including extracellular matrix, integrin binding, and activation of Src family tyrosine kinases at the dense body. Focal adhesion kinase is reported to be activated by mechanical stretch at dense bodies. This study provides a link between activation of L-type Ca²⁺ channels by the αβ₁ integrin and the Src family of tyrosine kinases in the control of vasomotor tone. Given the close association of ion channels, integrins and tyrosine kinases at the level of the dense body, it would seem plausible that this axis is involved in mechanotransduction in the myogenic response implicating integrins as the putative “sensors.”

Vessel injury is known to increase expression of the fibronectin variant targeted by the LDV sequence. It is proposed that the ability of the αβ₁ integrin to alter vasomotor tone through modulation of L-type Ca²⁺ channel conductance may be involved in responses to tissue injury. This study supports an involvement of integrins in the control of vascular tone, but a specific link between integrins and myogenic signaling is yet to be determined. Whether L-type Ca²⁺ channel function can be modulated by mechanical forces transmitted through the integrin-extracellular matrix needs to be demonstrated. A number of questions remain but further studies in which the components of the myogenic response can be isolated from those involved in agonist-induced contractions will help to provide further insight into this complex process.

References


**Key Words:** myogenic response | arteriolar constriction | mechanotransduction | cytoskeleton | L-type Ca²⁺ channels
Can Integrins Integrate Vascular Myogenic Responses?
Livia C. Hool

doi: 10.1161/01.RES.0000012916.66975.26

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/90/4/371

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/