The pathogenesis of essential hypertension is multifactorial. Although the cause of elevated arterial pressure is unknown in most cases, the fundamental hemodynamic abnormality in hypertension is increased peripheral resistance primarily due to changes in vascular structure and function. These changes include arterial wall thickening and abnormal vascular tone, which are modulated by complex interactions between susceptibility genes and environmental factors influencing neural, humoral, cellular, and subcellular mechanisms. While essential hypertension likely has a number of distinct causes, identification of a common feature of mechanisms. While essential hypertension likely has a number of distinct causes, identification of a common feature of hypertension may provide a useful target to treat the disease. The present study by Northcott et al in this issue of Circulation Research reports an alternation in an intracellular signaling that may contribute to deregulated vascular tone and remodeling during hypertension.

**PI3K Signal Transduction Pathway**

In the last few years, the PI3K signal transduction pathway has emerged as one of the main signal routes that coordinate complex events leading to changes in cell metabolism, cell growth, cell movement, and cell survival. Growth factors, cytokines, and insulin, as well as attachment of cells to the extracellular matrix, stimulate the recruitment of a family of lipid kinases known as phosphoinositide 3-kinase (PI3K) to the plasma membrane (Figure). The activated PI3K converts the plasma membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP$_2$) to phosphatidylinositol-3,4,5-trisphosphate (PIP$_3$). Signaling proteins with pleckstrin-homology (PH) domains, such as the serine/threonine protein kinases, protein kinase B (PKB, also known as Akt), phosphoinositide-dependent kinase-1 (PDK-1) and PDK-2, accumulate at sites of PI3K activation. Association with PIP$_3$ at the membrane brings these proteins into proximity and facilitates phosphorylation of Akt by PDK-1 and PDK-2. The activated Akt phosphorylates a host of other proteins that affect cell growth, cell cycle entry, and cell survival.

**Roles of PI3K Signaling in Endothelial Cells**

Recent evidence indicates that PI3K signaling mediates survival signals of many angiogenic factors, including vascular endothelial growth factor (VEGF), hepatocyte growth factor, and angiopoietin. Since it was demonstrated that Akt phosphorylates endothelial nitric oxide (eNOS) at Ser1177 and Ser1179, many studies reported that the PI3K/Akt signaling pathway mediates rapid nongenomic eNOS activation and consequent vasodilation by VEGF, estrogen, corticosteroid, and shear stress. The PI3K/Akt signaling in endothelial cells plays central roles in the regulation of vascular homeostasis and angiogenesis.

**Roles of PI3K Signaling in Smooth Muscle Cells**

Recent reports revealed that PI3K/Akt signaling also plays important roles in vascular smooth muscle cells (VSMCs). PI3K/Akt signaling mediates cell survival, proliferation, and migration of VSMCs induced by insulin-like growth factor-1 (IGF-1). Recently, it was demonstrated that 1α,25-dihydroxyvitamin D induces VSMC migration via activation of PI3K. The PI3K/Akt pathway is also required for IGF-1 and platelet-derived growth factor (PDGF) to maintain the differentiated phenotype of VSMCs. Angiogenesis II induces VSMC hypertrophy and polyploidy in a PI3K/Akt-dependent manner. These reports suggest that the PI3K signaling pathway plays critical roles in pathological accumulation of VSMCs observed in various types of vascular lesions.

**Potential Role of PI3K in the Pathogenesis and Pathology of Hypertension**

Northcott et al found that arteries from two models of hypertension develop spontaneous tone, which is eliminated by PI3K inhibitors LY294002 and wortmannin. Aorta from hypertensive rats showed enhanced PI3K activity, which was associated with increased expression of PI3K subunits, p110α and p110β. In general, Akt mediates many of the downstream events controlled by PI3K. Notably, the phosphorylation level of Akt was significantly lower in hypertensive rats, indicating that Akt does not mediate spontaneous tone development induced by PI3K activation. Then, how does PI3K activation cause spontaneous tone?

It is well known that smooth muscle contraction is regulated by intracellular Ca$^{2+}$ concentration. The global rise in intracellular Ca$^{2+}$ initiates actin-myosin interaction by activating myosin light chain kinase (MLCK). To clarify the link between PI3K and Ca$^{2+}$ handling, Northcott et al demonstrate that LY294002, like a L-type Ca$^{2+}$ blocker, abolished Ca$^{2+}$-induced spontaneous tone in aorta of hypertensive rats, whereas LY294002 had no effect on the enhanced contraction induced by BayK8644, a direct L-type channel agonist. LY294002 also corrected KCl or norepi-
Potential involvement of PI3K in vascular smooth muscle contraction. Binding of growth factors or insulin to specific receptors stimulates tyrosine kinase, which leads to recruitment of phosphatidylinositol 3-kinase (PI3K) to the plasma membrane and subsequent activation. PI3K can also be stimulated by integrin-dependent cell adhesion and by G protein–coupled receptors. The activated PI3K converts the plasma membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP$_2$) to phosphatidylinositol-3,4,5-triphosphate (PIP$_3$). PTEN is an endogenous phosphatase for PIP$_3$. Signaling proteins with pleckstrin-homology (PH) domains accumulate at sites of PI3K activation. PDK-1 and PDK-2 phosphorylate Akt. Ca$^{2+}$ enters cells via L-type calcium channels. Ca$^{2+}$/calmodulin complex activates myosin light chain kinase (MLCK), which initiates actomyosin sliding by phosphorylating myosin light chain. PIP$_3$ may recruit unknown signaling proteins that interact with Ca$^{2+}$ channels. Wortmannin inhibits PI3K and MLCK. ECM indicates extracellular matrix; CaM, calmodulin.

neprine-induced contraction in hypertensive rats. Based on these observations, Northcott et al suggest that PI3K may activate L-type Ca$^{2+}$ channel and Ca$^{2+}$ flux. It is plausible that PIP$_3$ recruits unknown signaling proteins having PH domains, which interact with Ca$^{2+}$ channels. Alternatively, PI3K and/or PI3K-regulated signaling molecules might increase calcium sensitivity of VSMCs by interacting with MLCK or myosin light chain phosphatase. It is also possible that PI3K alters membrane depolarization, a main stimulus for Ca$^{2+}$ current through voltage-gated Ca$^{2+}$ channels.

Activation of PI3K/Akt signaling in endothelial cells functions to dilate vessels by increasing eNOS activity. Interestingly, Northcott et al found that LY294002 functioned to inhibit contraction in endothelium-intact aorta as well as in endothelium-denuded aorta. It is likely that endothelium-mediated vascular tone regulation is impaired during hypertension.

The present study may have further implication for the pathogenesis of vascular complication in patients with hypertension. Most untreated patients with hypertension develop arteriosclerotic lesions and further increase in arterial pressure. It is likely that the activated PI3K in VSMCs causes cell migration, proliferation, and hypertrophy, contributing to neointima formation in atherosclerosis and vascular remodeling during hypertension. Consistent with this notion, Hixon et al reported that VSMCs from spontaneous hypertensive rats displayed elevated PI3K/Akt activity with hypertrophy and polyploid nuclei, which are frequently observed in the vascular lesions of patients with hypertension.

Although Northcott et al propose a previously unrecognized role of PI3K in the pathophysiology of hypertension, a number of critical questions remain unanswered. Is the upregulation of PI3K a primary cause of hypertension or a secondary phenomenon in response to elevated arterial pressure? What kind of humoral and/or mechanical stimuli do activate PI3K in VSMCs? Further studies would be required to dissect the roles of PI3K in the pathophysiology of hypertension and to find therapeutic strategies for hypertension targeting PI3K and/or PI3K-regulated intracellular signaling molecules.

References


**KEY WORDS:** phosphatidylinositol 3-kinase • Akt • hypertension • smooth muscle • endothelial cells
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Circ Res. 2002;91:273-275
doi: 10.1161/01.RES.000031956.29928.62
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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