The adaptive remodeling of cerebral arteries, including hypertrophy (medial thickening) and eutrophy (luminal narrowing), is a prominent feature of hypertension and a major risk factor for stroke. Multiple mechanisms, such as arterial smooth muscle cell (SMC) proliferation, migration and apoptosis, endothelial cell dysfunction, inflammation, and fibrosis, have been implicated in structural remodeling in response to chronic hypertension. Although the hypertrophic increase in cell volume of arterial SMCs is the primary mechanism for the thickening of mesenteric arterial media in spontaneously hypertensive rats and of cerebral arteries in the 2-kidney, 2-clip renal hypertensive rats, the impact of the hypertension-induced changes in cell volume of the arterial SMCs and its clinical significance are still unknown.

Alterations in cell volume are common adaptive mechanisms of most mammalian cells, including arterial SMCs, in response to metabolic, osmotic, and/or static pressure perturbations. Cells are able to precisely maintain their size through the regulated loss or gain of intracellular ions or other osmolytes to avoid excessive alterations of cell volume that may jeopardize structural integrity and a variety of cellular functions. Acute increase in cell volume will initiate the regulatory volume decrease process to bring the cells back to their initial volume, which is achieved by the opening of volume-regulated Cl⁻ channels (VRCCs) and other channels and transporters mediating Cl⁻, K⁺, and taurine efflux. As one of the most important mechanisms for cell volume homeostasis, activation of VRCCs has been implicated in a number of vital cellular functions involved in hypertension-induced vascular remodeling, including the regulation of membrane potentials, vascular myogenic tone, cell proliferation, migration, and apoptosis (Figure). For example, high blood pressure-induced depolarization and contraction of cerebral artery smooth muscle may be partially mediated by VRCCs. There is evidence that the magnitude of VRCC currents in actively growing vascular SMCs is higher than in growth-arrested or differentiated SMCs, suggesting that VRCCs may be important for SMC proliferation. Therefore, hypertension-induced increase in cell volume and activation of VRCCs may contribute to the structural and functional remodeling through an integrated regulation of multiple cellular functions.

The short isoform of CIC-3, a member of the CIC superfamily of voltage-dependent Cl⁻ channels, has been proposed to be the molecular correlate of a key component of the native VRCCs in cardiac myocytes and vascular SMCs. A series of recent independent studies from many laboratories further strongly corroborated this hypothesis (please see recent reviews by Duan and Hume et al). It has been demonstrated that CIC-3 is expressed in aortic, pulmonary, and cerebral artery SMCs of many species, including humans. Knockdown of CIC-3 by small interfering RNA, short hairpin RNA, and antisense and intracellular dialysis of anti-CIC-3 antibody all consistently eliminated VRCC currents in many types of cells. Recent accumulating evidence suggests an important role for CIC-3 and VRCCs in the regulation of cell proliferation induced by hypertrophic alternations in cell volume. A recent study found that static pressure increased VRCCs and CIC-3 expression and promoted rat aortic vascular SMC proliferation and cell cycle progression. Inhibition of VRCCs with pharmacological blockers (eg, diphenyleneiodonium) or knockdown of CIC-3 with CIC-3 antisense oligonucleotide dramatically inhibited pressure evoked cell proliferation and cell cycle progression of rat aortic SMCs. These data suggest that CIC-3 and VRCCs may play a critical role in static pressure-induced cell proliferation and cell cycle progression. Because arterial SMC proliferation is a key event in the development of hypertension-associated vascular disease, CIC-3 and VRCCs may be of unique therapeutic importance for the treatment of hypertension-attendant vascular complications.

Recent studies have demonstrated that statins are effective in attenuating vascular remodeling, although the underlying mechanisms are still not determined. In this issue of Hypertension, Liu et al used integrated, multiple approaches and performed a thorough investigation on the effects of simvastatin on the hypertension-induced cerebrovascular remodeling and VRCCs in basilar SMCs. They first demonstrated that simvastatin improved the hypertension-caused cerebrovascular remodeling in 2-kidney, 2-clip renal hypertensive rats. Then they used cultured rat basilar SMCs to further study the effects of simvastatin on cell proliferation and the whole-cell VRCC current and volume-regulated Cl⁻ movement. They found that simvastatin inhibited cell proliferation and also the volume-regulated chloride movement and VRCCs, which could be abolished by pretreatment of the cells with meval-
ClC-3, a member of the voltage-gated ClC Cl⁻ channel family, encodes Cl⁻ channels in vascular SMCs that are volume regulated (i_{Cl,vol}) and can be activated by cell swelling (i_{Cl,swell}) induced by exposure to hypotonic extracellular solutions or possibly membrane stretch. i_{Cl,swell} is a basally activated ClC-3 Cl⁻ current. α-Helices of ClC-3 are shown as α-r (see review by Duan1). ClC-3 proteins are expressed on both the sarcolemmal membrane and intracellular organelles including mitochondria (mito) and endosomes. The proposed model of endosome ion flux and function of Nox1 and ClC-3 in the signaling endosome is adapted from Miller et al8 Binding of interleukin (IL)-1 receptor (IL-1R) with IL-1α or tumor necrosis factor (TNF)-α to the cell membrane initiates endocytosis and formation of an early endosome (EEA1 and Rab5), which also contains Nox subunits Nox1 and p22phox, in addition to ClC-3. Nox1 is electrogenic, moving electrons from intracellular NADPH through a redox chain within the membrane initiates endocytosis and formation of an early endosome (EEA1 and Rab5), which also contains Nox subunits Nox1 and p22phox, in addition to ClC-3. Nox1 is electrogenic, moving electrons from intracellular NADPH through a redox chain within the membrane.

ClC-3 overexpression would antagonize the inhibitory effect of simvastatin on cell proliferation. Indeed, they found that increased ClC-3 activity diminished the inhibitory effect of simvastatin on cell proliferation. As a charged and short-lived anion, it is believed that superoxide flux is insufficient to initiate intracellular signaling because of the combination of poor permeability through the phospholipid bilayer and a rapid dismutation to its uncharged and more stable derivative, hydrogen peroxide. Recent studies have also shown that ClC-3 may also function as an antiapoptotic mechanism through regulation of cell volume and intracellular pH and as a regulator of other transport functions involved in the etiology of hypertension (Figure).8

Whether the beneficial effects of statins could be attributed also to their effects on these cellular functions of ClC-3 in cerebrovascular SMCs during hypertension is still an unanswered question. Nevertheless, regulation of ClC-3 functions
in the cardiovascular system is emerging as a novel and important mechanism for the structural remodeling of the vasculature and may provide a novel therapeutic approach for the treatment of many vascular diseases, such as hypertension and stroke.

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None.

**References**


Volume Matters: Novel Roles of the Volume-Regulated CIC-3 Channels in Hypertension-Induced Cerebrovascular Remodeling

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