TRP Proteins
A New Dimension in the Treatment of Occlusive Vascular Disease

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In this issue of *Circulation Research*, Beech and collaborators report their exciting discovery that blockade of the TRPC1 channel inhibits the salient features of vascular disease: smooth muscle cell proliferation and neointima formation. The idea of using Ca\(^{2+}\) channel blockers as therapy for vascular disease was introduced in the late seventies and led to a large body of literature. Calcium antagonists originally were introduced as antiischemic and antihypertensive drugs, but were also found to reduce the development of intimal lesions in many animal models of atherosclerosis. After injury caused by angioplasty or venous coronary bypass grafting, occlusive vascular diseases such as atherosclerosis, neointimal hyperplasia, and restenosis stem from an adaptive reaction of the blood vessels to local injury and altered conditions of blood flow, which involves a shift of smooth muscle cells from contractile to synthetic phenotype characterized by activation of smooth muscle cell proliferation and migration. These processes involve various proliferation signal cascades such as Akt, MAPK, and cadherin/\(\beta\)-catenin. There is substantial support for a central regulatory role of intracellular Ca\(^{2+}\) in these processes, and many publications support the effectiveness of calcium antagonists in reducing smooth muscle proliferation.

However, the term “calcium antagonist” refers exclusively to blockers of L-type voltage gated Ca\(^{2+}\) channels (VGCC), and 3 decades of experience with these agents have led to limited success in easing the ravages of occlusive vascular disease. This disappointment appears to be related to 3 relevant characteristics of calcium antagonists. First, in the vasculature their primary target is the VGCC of resistance arteries, blockade of which leads to lowered peripheral resistance and complications such as peripheral edema and headache. Second, calcium antagonists are not tissue specific and their cardiac effects include negative inotropy and chronotropy, thus rendering them less than optimal in cases of heart failure. Finally, L-type channels may not play an important role in vascular remodeling as they are downregulated during dedifferentiation, which is characteristic of proliferative vascular disease after arterial injury associated with invasive procedures like angioplasty and vein bypass grafting.

The discovery of the new class of Ca\(^{2+}\) channels, Receptor Operated Ca\(^{2+}\) Channels or ROCs, broadened the vision of vascular Ca\(^{2+}\) signaling, implicating multisite and multifunctional control. Dynamic and versatile Ca\(^{2+}\) signaling observed in all vascular cells is dependent on the presence of diverse Ca\(^{2+}\) channels, exchangers, and pumps arranged in unique ultrastructural arrays in cell and organelar membranes. Such specialization of expression and localization is capable of not only controlling membrane potential, but of creating cytoplasmic microdomains near specific Ca\(^{2+}\)-sensitive enzymes, which can control biochemical pathways and/or regulate gene expression (Figure). ROCs were originally defined as being activated by neurotransmitters, hormones, and autacoids, without a requirement for depolarization. However, receptor activation can lead to channel opening by three well recognized mechanisms, leading to the following functional Ca\(^{2+}\) channel classifications: (1) direct activation by an extracellular ligand (LGCC), (2) activation by a second messenger (SMOCC), or (3) activation by intracellular Ca\(^{2+}\)-store depletion (SOC). More recently it has been recognized that the molecular building blocks of the broad class of ROCs are homologues of Drosophila transient receptor potential protein (TRPs), and at least 28 mammalian TRP homologues have been identified based on sequence homology to the drosophila TRPs. The TRP channel proteins and their role in smooth muscle Ca\(^{2+}\) regulation has recently been expertly discussed by Beech, the author of this issue’s article. Although association of the functional types of ROCs with specific TRP complexes is only in its infancy and the nomenclature is still developing, the great variety of TRP proteins plus the fact that native TRP channels might be both homomeric and heteromeric holds the promise of providing numerous, specific targets for the development of therapeutic agents selective for various types of vascular disease.

Indeed, Beech and coworkers have provided proof of principle for TRPC1 blockade in the treatment of vascular injury because expression of TRPC1 is enhanced in injured vascular smooth muscle and the neointima and its blocking antibody (T1E3) reduced neointima formation in the human saphenous vein, without apparent suppression of endothelial function. Targeting TRPC1 as a therapeutic approach to occlusive vascular disease could have the considerable advantage of separating the antiproliferative effects of Ca\(^{2+}\)-entry blockade from those of lowering peripheral resistance and cardiac output as seen with the classical calcium antag-
Differential expression and localization of Ca\(^{2+}\) channels and pumps determines function-specific Ca\(^{2+}\) signals. Without specifying mechanisms, the above scheme illustrates the concept that selective activation of a variety of Ca\(^{2+}\) and Na\(^+\) transporters strategically arranged in the plasma membrane, SR, and mitochondria yields a variety of Ca\(^{2+}\) transients, characterized by unique spatiotemporal patterns. Such variable Ca\(^{2+}\) signals allow smooth muscle cells to differentially regulate contraction, migration, proliferation, and apoptosis. This concept of "site and function specific Ca\(^{2+}\) signaling" provides the theoretical basis for therapeutic targeting of specific Ca\(^{2+}\) channels, pumps, or exchangers to selectively inhibit smooth muscle proliferation.

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References


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