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Smooth Muscle Cell Ca^{2+} : Think Locally, Act Globally

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Abstract

Dynamic changes in intracellular Ca^{2+} levels in vascular smooth muscle cells are critically important for cardiovascular regulation. This Special Topic Issue highlights a series of expert opinion articles focused on this important subject. After a brief overview, novel discoveries surrounding smooth muscle cell Ca^{2+} influx via L-type and T-type channels are reviewed. Current work revealing the functional importance of dynamic Ca^{2+} signaling in the control of the parenchymal microvasculature and the emerging role of mitochondrial Ca^{2+} signaling and store-operated Ca^{2+} entry in smooth muscle cells is discussed. Finally, recent data describing a new target of localized Ca^{2+} signaling in arterial myocytes that is responsible for membrane depolarization is reviewed. Authors were encouraged to write in an opinionated and provocative manner with the hope of stimulating discussion in this area of research.

Keywords

Smooth muscle cell; vascular; Ca^{2+}

INTRODUCTION

Smooth muscle cells are oriented circumferentially within the vascular wall. Contraction or relaxation of these cells in response to appropriate stimuli, such as endothelium-dependent vasodilators, changes in intraluminal pressure, or receptor-dependent vasoconstrictor agonists, influences cardiovascular control. For example, in small arteries and arterioles, slight changes in myocyte contractility alter luminal radius with significant effects on vascular resistance and localized blood flow. Altered contractility of venous smooth muscle cells changes the compliance of these vessels to influence venous return and cardiac output. Ca^{2+} ions have long been known to be essential for muscular activity [7], and in smooth muscle cells, increases in *global* intracellular $[\text{Ca}^{2+}]$ activate signaling pathways leading to myocyte contraction. However, we now know that this is not the whole story, and changes in intracellular Ca^{2+} that are restricted in space and time significantly contribute to smooth muscle cell function. These discoveries were initially stimulated by the development of a new generation of Ca^{2+} indicator dyes allowing direct and simultaneous measure of Ca^{2+} levels within intracellular compartments of living contractile smooth muscle [5,17]. Further technological advancements in confocal microscopy and the development of a new

generation of fast fluorescent Ca^{2+} indicators provided significant improvement in the spatiotemporal resolution of Ca^{2+} signals [8,11]. By applying these techniques for the first time to contractile smooth muscle cells, Nelson and colleagues observed novel, transitory subcellular Ca^{2+} signals called “ Ca^{2+} sparks” [15]. Ca^{2+} sparks result from the release of Ca^{2+} from the sarcoplasmic reticulum and generate microdomains where Ca^{2+} levels are transiently 1–3 orders of magnitude greater than that of the surrounding cytosol. More interestingly, Ca^{2+} sparks are functionally coupled to multiple large conductance Ca^{2+} -activated K^+ (BK_{Ca}) channels on the plasma membrane. Multiple BK_{Ca} channels are activated by each Ca^{2+} spark, resulting in the generation of macroscopic outward K^+ currents that hyperpolarize the sarcolemma. Furthermore, blocking Ca^{2+} spark activity causes arterial constriction, indicating that *localized* increases in Ca^{2+} can cause vasodilation by activating hyperpolarizing currents. This ground-breaking discovery inspired subsequent generations of scientists to investigate the physiological and pathophysiological ramifications of subcellular Ca^{2+} signaling in greater detail. Application of cutting-edge technology, including total internal fluorescence reflection microscopy (TIRFM) [14], multiphoton intravital microscopy [9], and transgenic mice expressing genetically encoded Ca^{2+} indicators [12], is now further advancing this field. In addition to regulating contractility and membrane potential, Ca^{2+} signals in smooth muscle cells are now understood to influence gene expression and cellular proliferation [2]. Increased understanding of Ca^{2+} signaling processes in vascular myocytes under normal and pathophysiological conditions is likely to provide significant insight into cardiovascular diseases involving these cells, perhaps leading to new therapeutic strategies.

This special topics issue (STI) of *Microcirculation* is focused on intracellular Ca^{2+} dynamics in vascular smooth muscle cells. A brief introduction to this topic is provided by Amberg and Navedo [1]. Novel discoveries surrounding Ca^{2+} influx pathways in smooth muscle cells are described by Navedo and Amberg (L-type Ca^{2+} channel sparklets) [13] and Harraz and Welsh (T-type Ca^{2+} channels) [6]. Dabertrand, *et al.* discuss their recent elegant work revealing the functional importance of smooth muscle cell Ca^{2+} signaling in the control of cerebral blood flow in the parenchymal microvasculature [3]. McCarron and coworkers provide insight into the emerging role of mitochondrial Ca^{2+} signaling in smooth muscle cells [10]. Trebak *et al.* discuss the role of store-operated Ca^{2+} in smooth muscle cells [16]. Finally, Gonzales and Earley discuss a recently described target of localized Ca^{2+} signaling in arterial myocytes that is responsible for membrane depolarization [4].

PERSPECTIVE

This editorial comment introduces a Special Topics Issue of the Journal entitled “Smooth Muscle Cell Ca^{2+} ”.

Acknowledgments

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