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Review article

Ca^{2+} Clearance and contractility in vascular smooth muscle: Evidence from gene-altered murine models

Brian Oloizia, Richard J. Paul*

Department of Molecular and Cellular Physiology, University of Cincinnati College of Medicine, Cincinnati, OH 45267-0576, USA

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Abstract

The central importance of calcium clearance proteins, and their regulators, in the modulation of myocardial contractility and intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) has long been established. Key players identified include the Na^+–Ca^{2+} exchanger, the Na^+–K^+ ATPase, the sarco(endo) plasmic reticulum Ca^{2+}-ATPase and associated phospholamban. Gene-targeted and transgenic murine models have been critical in the elucidation of their function. The study of these proteins in the regulation of contractile parameters in vascular smooth muscle, on the other hand, is less well studied. More recently, gene-targeted and transgenic models have expanded our knowledge of Ca^{2+} clearance proteins and their role in both tonic and phasic smooth muscle contractility. In this review, we will briefly treat the mechanisms which underlie Ca^{2+} clearance in smooth muscle. These will be addressed in light of studies using gene-modified mouse models, the results of which will be compared and contrasted with those in the cardiomyocyte. The recently identified human mutations in phospholamban, which lead to dilated cardiomyopathy, are also present in vascular and other smooth muscle. Given the importance of these Ca^{2+} clearance systems to modulation of smooth muscle, it is likely that mutations will also lead to smooth muscle pathology.

Keywords: Calcium clearance; Gene-altered mice; Na^+-K^+ ATPase; Na^+–Ca^{2+} exchange; Plasma membrane Ca^{2+}-ATPase; Sarco(endo)plasmic reticulum Ca-ATPase; Phospholamban; Vascular smooth muscle; Heart; Contractility

Contents

1. Ca^{2+} clearance and regulation of $[Ca^{2+}]_i$

Ca^{2+} homeostasis is central to the regulation of smooth muscle function. It is well established that $[Ca^{2+}]_i$ plays an

* Corresponding author. Tel.: +1 513 558 3032; fax: +1 513 558 5738.
E-mail address: paulrj@ucmail.uc.edu (R.J. Paul).

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essential role in the activation of myosin light chain kinase, which phosphorylates myosin, thereby activating the actin-myosin interaction (for review see [1]). It has also been estimated that Ca^{2+} influx under basal conditions is 16 μmole/l per minute, more than 2 orders of magnitude greater than the resting $[Ca^{2+}]_i$. Thus Ca^{2+} clearance from the cytosol is critical to the maintenance of a quiescent baseline and is a major factor in modulation of Ca^{2+} homeostasis and thus contractile force. The plasma membrane Ca^{2+} ATPase (PMCA), sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA), Na^+–Ca^{2+}-exchanger (NCX) and mitochondria all function to some extent in this process (for reviews see [2,3]). Fig. 1 shows a schematic illustration of these Ca^{2+} clearance pathways. Also of importance to smooth muscle Ca^{2+} clearance are phospholamban (PLN), an endogenous inhibitor of SERCA, and the Na^+-K^+ ATPase (NKA), which couples to NCX, and facilitates the extrusion of Ca^{2+} via the forward mode of the exchanger. NCX is generally considered to be a high-capacity exchanger, i.e., low affinity for Ca^{2+} ($K_d \approx 1$ μM), but high turnover [4–7]. SERCA and PMCA, on the other hand, have a higher affinity for Ca^{2+} ($K_d \approx 0.1$–0.3 μM) [6,8–11], but lower turnover than NCX. For smooth muscle, the relative contribution of each to Ca^{2+} clearance is dependent on conditions and smooth muscle type, but in general, NCX accounts for about 60%, while PMCA and SERCA facilitate about 20–30% each. Mitochondrial Ca^{2+} uptake can also be a factor under certain conditions, but its apparent affinity is thought to be relatively low (~10–20 μM, [12]). Recent evidence, however, suggests mitochondria may play some role as both a buffer and/or regulator of Ca^{2+} clearance [13,14].

Much recent interest has been directed toward the role of caveolae, and their corresponding subsarcolemmal compartments, in smooth muscle Ca^{2+} handling. Caveolae $[Ca^{2+}]$ may, at least transiently, differ from that of the general extracellular milieu (for review see [15,16]). Localized to regions of the plasma membrane closely associated with the peripheral sarco-(endo)plasmic reticulum (SR), these vesicular membrane structures have been suggested to be a source of Ca^{2+} that can be recycled to and from the SR, and therefore have been implicated in excitation-contraction coupling. Localization of PMCA, NCX and voltage-dependent calcium channels (VDCC) to this compartment has been firmly established in smooth muscle ([15,17], Fig. 1). Colocalization of these Ca^{2+} handling proteins with caveolae suggest a role for Ca^{2+} extrusion and regulation in this subsarcolemmal compartment. Indeed, it is hypothesized that both caveolae, via L-type Ca^{2+} channels, and SR, via ryanodine receptors (RyRs), can supply the subsarcolemmal space with Ca^{2+}, while either NCX or PMCA are involved in its extrusion from caveolae. The SERCA pump, on the other hand, could be used to sequester such Ca^{2+} into the SR pool. While the NKA has been observed in association with caveolae in cardiac muscle [18], there is currently no direct evidence for its colocalization in the caveolae of smooth muscle. The colocalization of NCX and the α2-isoform of NKA in smooth muscle ([19,20], Fig. 1), however, suggests that such an association may indeed exist. The structure of the SR itself can also be a factor in this interaction complicating this picture. Whether it is a single structure or multiple vesicles has long been debated with the most recent evidence favoring a single entity [21].

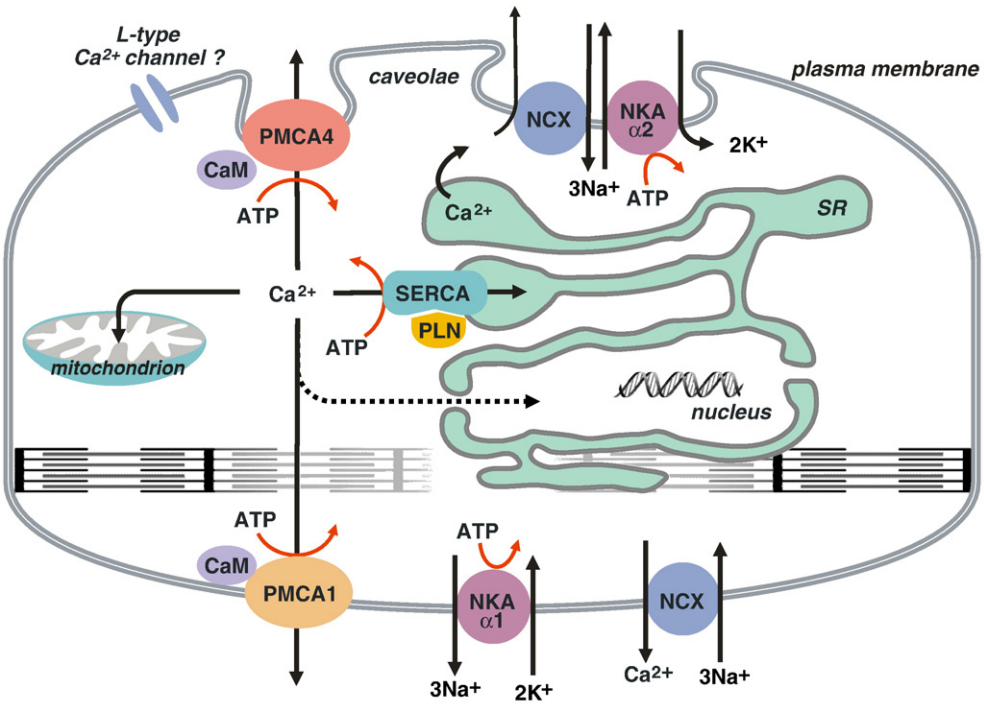

Fig. 1. Schematic overview of the Ca^{2+}-clearance systems associated with smooth muscle. These include the plasma membrane Ca^{2+} ATPase isoforms (PMCA1 and 4), the plasma membrane Na^+–Ca^{2+} exchanger (NCX) coupled to the Na^+-K^+ ATPase (α-isoforms 1 and 2) and the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA isoforms 2a and 2b). Mitochondria are also included, though their role in Ca^{2+} clearance is not known with certainty. Adapted from Ishida and Paul [2].