HHS Public Access

Author manuscript

Adv Pharmacol. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Adv Pharmacol. 2017 ; 78: 49–87. doi:10.1016/bs.apha.2016.08.002.

Calcium Channels in Vascular Smooth Muscle

D. Ghosh[*], **A.U. Syed**[*], **M.P. Prada**[*], **M.A. Nystoriak**[†], **L.F. Santana**[*], **M. Nieves-Cintrón**[*], and **M.F. Navedo**[*,1]

[*]University of California, Davis, CA, United States

[†]Diabetes and Obesity Center, University of Louisville, Louisville, KY, United States

Abstract

Calcium (Ca^{2+}) plays a central role in excitation, contraction, transcription, and proliferation of vascular smooth muscle cells (VSMs). Precise regulation of intracellular Ca^{2+}concentration ($[Ca^{2+}]_i$) is crucial for proper physiological VSM function. Studies over the last several decades have revealed that VSMs express a variety of Ca^{2+}-permeable channels that orchestrate a dynamic, yet finely tuned regulation of $[Ca^{2+}]_i$. In this review, we discuss the major Ca^{2+}-permeable channels expressed in VSM and their contribution to vascular physiology and pathology.

1. INTRODUCTION

Highly coordinated control of VSM excitability is essential for proper vascular function and regulation of blood flow. Intracellular Ca^{2+} plays a pivotal role in this process. Accordingly, well-orchestrated and distinct signaling pathways allow tight regulation of $[Ca^{2+}]_i$,which, together with differential Ca^{2+} sensitivity of the contractile machinery, provide additional fine-tuning of VSM contractility. Studies over the last several decades have revealed the expression of multiple Ca^{2+}-permeable channels in VSM that coordinate a dynamic and precise control of $[Ca^{2+}]_i$, thereby playing a pivotal role in VSM physiology (Fig. 1). Changes in $[Ca^{2+}]_i$ are produced by Ca^{2+} influx through voltage-dependent and -independent plasmalemmal Ca^{2+}-permeable channels, as well as Ca^{2+} release from intracellular stores. L-type CaV1. channels (LTCCs) have long been considered the primary route of Ca^{2+} entry in VSM. Indeed, Ca^{2+} influx through LTCCs is the principal mediator of myogenic response, which is the intrinsic ability of VSM to contract/relax in response to changes in intraluminal pressure (Bayliss, 1902). Besides LTCC, T-type Ca^{2+} channels (TTCCs) are emerging as important contributors to myogenic tone. LTCCs also play a crucial role in excitation–transcription coupling in VSM (Amberg & Navedo, 2013). Members of the transient receptor potential (TRP) channel family, as well as Ca^{2+} release-activated channels (Orai/STIM), have also been found to contribute to regulation of VSM function. Moreover, Ca^{2+} release from intracellular stores through ryanodine receptors (RyRs) and inositol-1,4,5,-trisphosphate receptors (IP_3Rs) in the sarcoplasmic reticulum (SR) is an important contributor to $[Ca^{2+}]_i$ and VSM excitability. RyRs and IP_3Rs are also

[1]corresponding author: mfnavedo@ucdavis.edu.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

involved in VSM regulation via their communication with plasmalemmal ion channels. Recently, mitochondria have also been receiving substantial attention for their emerging relevance in VSM Ca^{2+} handling. This review presents an overview of the major Ca^{2+}-permeable channels that contribute to VSM Ca^{2+} handling and contractility, and vascular reactivity. More extensive reviews on individual channels can be found elsewhere (Amberg & Navedo, 2013; Earley & Brayden, 2015; Harraz & Welsh, 2013b; McCarron, Olson, Wilson, Sandison, & Chalmers, 2013; Narayanan, Adebiyi, & Jaggar, 2012; Navedo & Amberg, 2013).

2. PLASMALEMMAL Ca^{2+}-PERMEABLE CHANNELS

2.1 Voltage-Dependent Calcium Channels

Voltage-dependent Ca^{2+} channels (VDCCs) are widely expressed among excitable cells and display a diversity of electrophysiological properties, which allows them to influence many physiological functions (Catterall, 2011). Since their initial discovery in 1953, multiple VDCC subtypes have been characterized (Catterall, 2011). Of particular importance to this review are the LTCCs, which exhibit a large-conductance and long-lasting current with membrane depolarization, and TTCCs with tiny conductance and transient current at negative potentials. N-, P/Q-, and R-type Ca^{2+} channels have also been identified (Catterall, 2011). In the following section, we focus on LTCCs and TTCCs and their contribution to $[Ca^{2+}]_i$ in VSM.

2.1.1 L-Type $Ca_V1.2$ Channels—LTCCs form the fulcrum in Ca^{2+} dynamics of NVSM. Ca^{2+} influx through LTCCs in these cells is a principal mediator of myogenic tone (Fig. 1) (Amberg & Navedo, 2013; Knot & Nelson, 1998; Nelson, Patlak, Worley, & Standen, 1990). The vascular LTCC was first sequenced from rabbit lungs in 1990 (Biel et al., 1990), showing 65% amino acid sequence homology with its skeletal muscle isoform. LTCCs are comprised of pore-forming α_{1c} and auxiliary β, $\alpha_2\delta$, and γ subunits that modulate channel function. The α_{1c}, which contains the voltage sensor, the gating apparatus, and the Ca^{2+}-permeable pore, is made up of four homologous domains (I, II, III, IV), each of which is composed of six transmembrane segments (S1–S6) and intracellular NH_2- and COOH-termini. The S5 and S6 of each homologous domain form the pore region of the channel. Two glutamate residues at the pore loop determine the Ca^{2+} selectivity. The S1–S4 forms the voltage sensor, which rotates to open the ion pore (Bezanilla, 2008).

The α_{1c} transcript undergoes extensive alternative spicing, which provides structural and functional diversity in cell-type selective expression patterns. For example, splice variation in rat α_{1c} exon-1 gives rise to arterial VSM specific α_{1c} subunit that has cysteine-rich NH_2-terminus (Cheng et al., 2007). This α_{1c} when coexpressed with only $\alpha_2\delta$ demonstrated more negative steady-state activation and deactivation kinetics, smaller whole-cell currents, and decreased plasmalemma incorporation. LTCCs containing a SM-selective 25 amino acid exon 9a in the I–II intracellular linker region exhibit more hyperpolarized window current and are a key regulator of cerebrovascular constriction (Liao et al., 2007; Nystoriak, Murakami, Penar, & Wellman, 2009). Other variations, which exclude exon 33, have

window current closer to resting membrane potential and higher sensitivity to blockade by nifedipine (Liao et al., 2007).

The COOH-terminus of α_{1c} provides regulatory functions such as plasmalemma targeting, retention, and constitutive intracellular recycling of LTCCs (Catterall, 2011). It also contains the calmodulin (CaM)-binding site, which facilitates channel trafficking to the plasmalemma. In rat and human cerebral arteries, the COOH-terminus of α_{1c} is cleaved, producing a short LTCC and a 50-kDa COOH-terminus fragment (Bannister et al., 2013). This fragment can be detected in the cytosol and the nucleus of VSM and was shown to induce vasodilation by decreasing α_{1c} expression and shifting the channel voltage dependence of activation to more depolarized potentials. Such findings warrant the need for further in-depth research regarding the role of the α_{1c} COOH-terminal fragment in blood pressure regulation in physiological and pathological conditions.

In vitro and in vivo studies have established the critical role for α_{1c} in vascular function. For instance, dihydropyridine antagonists (e.g., nifedipine, isradipine, nicardipine) that selectively inhibit α_{1c} activity were found to abolish the pressure-induced increase in $[Ca^{2+}]_i$ and prevented the development of myogenic tone (Knot & Nelson, 1998). Conversely, dihydropyridine agonists (e.g., Bay K 8644) that specifically stimulate LTCC activity enhance the myogenic response (Hwa & Bevan, 1986). Furthermore, α_{1c} knockout (SMAKO) mice showed a dramatic drop in myogenic tone and mean arterial pressure (Moosmang et al., 2003). Swelling of VSM may also induce cell contraction through activation of LTCC. Reports from cerebral artery VSM, canine basilar artery VSM, and rat-tail artery VSM confirmed the involvement of LTCC α_{1c} in vasoconstriction to a hypo-osmotic challenge (Kimura et al., 2000; Welsh, Nelson, Eckman, & Brayden, 2000; Wijetunge & Hughes, 2007).

The β subunit is generally paired in a 1:1 stoichiometry with $Ca_V1.2\alpha_{1c}$. The β subunit is made up of two conserved core regions, akin to the Src-homology-3 (SH3) domain and the guanylate kinase domain. Four β sub-units, which are encoded by four different genes with several known splice variants, have been identified. Both biophysical properties and plasmalemmal insertion of $Ca_V1.2\alpha_{1c}$ can be distinctively regulated by different β isoforms (Catterall, 2011). In VSM, β_3 is the predominant β subunit, and a recent study concluded that it plays a critical role in upregulating LTCC activity and in the development of angiotensin II (ANG II)-induced hypertension (Kharade et al., 2013).

Initially thought to be distinct subunits, the $\alpha_2\delta$ subunit exists as a single subunit connected by a disulfide bond (Catterall, 2011). The δ portion is anchored to the plasmalemma, while the glycosylated extracellular α_2 domain interacts with the α_{1c} (Gurnett, De Waard, &Campbell, 1996). Three different $\alpha_2\delta$ isoforms have been identified ($\alpha_2\delta1$– $\alpha_2\delta3$). Heterologous coexpression of different $\alpha_2\delta$ isoforms with different α_{1c} and β subunits produced channels with distinct gating profiles and current densities, highlighting the important regulatory role of $\alpha_2\delta$ on channel function (Klugbauer, Lacinova, Marais, Hobom, & Hofmann, 1999). In cerebral VSM, $\alpha_2\delta$ is a crucial regulator of LTCC function as illustrated by decreased Ca^{2+} influx via LTCCs and vasodilation following $\alpha_2\delta1$ knockdown (Bannister et al., 2009). Furthermore, increased $\alpha_2\delta1$ mRNA and protein were observed in

cerebral VSM from spontaneously hypertensive rats (Bannister et al., 2012). These data, and the β subunit data discussed earlier, suggest that increased $\alpha_2\delta1$ and β3 expression enhances LTCC expression and function, thus contributing to augmented vasoconstriction during hypertension. Therefore, targeting the $\alpha_2\delta1$ and β3 may be a viable therapeutic approach to reverse/ameliorate increased vasoconstriction during hypertension.

Eight γ subunits have been identified. These subunits contain four transmembrane regions with intracellular NH_2- and COOH-termini. The first extracellular loop contains the conserved region of the GLWXXC amino acid motif, the most distinct feature of all the γ subunits (Catterall, 2011). The γ subunits also regulate biophysical and trafficking properties of the α_{1c} (Arikkath & Campbell, 2003). However, little is known about the function of the γ subunit on the regulation of LTCCs in VSM.

LTCCs are major targets of second messenger/kinase signaling cascades such as protein kinase A (PKA) and protein kinase C (PKC). Modulation of LTCC activity by these kinases ultimately contributes to control VSM function and vascular reactivity. The modulation of vascular LTCC activity by PKA is controversial. Activation of PKA in VSM has been reported to inhibit, potentiate, or has no effect on LTCC activity (see review by Keef, Hume, & Zhong, 2001). This contrasts with abundant and consistent data, indicating that agonists that stimulate PKA activity typically trigger vasodilation. Surprisingly, it was recently reported that an elevation in extra cellular D-glucose from 5 to 15–20 mM, which is similar to the glucose concentration typically observed in animal models of diabetes and human diabetic patients, potentiates LTCC activity in cerebral VSM via a mechanism that requires PKA (Navedo, Takeda, Nieves-Cintron, Molkentin, & Santana, 2010; Nystoriak et al., 2014). This increase in vascular LTCC activity was correlated with enhanced myogenic tone in response to elevated glucose, thus providing the first example, to our knowledge, of a PKA-mediated vasoconstriction. On the other hand, activation of PKC by phorbol esters and vasoconstrictors acting through G_q-coupled receptors (e.g., ANG II, endothelin-1) results in potentiation of vascular LTCC activity and vasoconstriction (Keef et al., 2001; Weiss & Dascal, 2015). Consistent with this, genetic ablation of PKC protected against ANG II-induced potentiation of LTCC activity and the development of hypertension (Nieves-Cintron, Amberg, Navedo, Molkentin, & Santana, 2008). These genetic studies found that PKC activity was also required for basal and persistent LTCC activity in some VSM (see later and Santana et al., 2008). An integrated view of the specific upstream pathways contributing to PKA- and PKC-mediated LTCC regulation remains to be fully elucidated. Further, work in this area may help to identify novel therapeutic targets to treat pathological conditions associated with LTCC dysfunction such as hypertension (Nieves-Cintron et al., 2008).

Studies combining classical electrophysiology with high-resolution total internal reflection fluorescence microscopy have provided important information regarding the spatial organization of functional LTCCs and resultant Ca^{2+} signal in VSM (Nystoriak, Nieves-Cintron, & Navedo, 2013). Using this approach, elementary Ca^{2+} influx events via LTCCs (i.e., LTCC sparklets) were imaged in VSM, and channel activity was found to occur through distinct loci of low and high activity (Navedo, Amberg, Votaw, & Santana, 2005). The molecular, biophysical, and regulatory properties as well as the functional role of LTCC

sparklets in VSM have been extensively reviewed in recent papers (Navedo & Amberg, 2013; Navedo & Santana, 2013; Santana & Navedo, 2009).

LTCC sparklets are sensitive to dihydropyridines and extracellular Ca^{2+} concentration and insensitive to store depletion by thapsigargin. Noteworthy, LTCC sparklets are always associated with inward L-type Ca^{2+} currents, confirming that they are produced by Ca^{2+} influx via LTCC. Whereas low activity LTCC sparklets exhibit stochastic behavior, high activity LTCC sparklets are produced by prolonged channel openings and in many cases by the nonstochastic, coordinated opening of clustered LTCC channels (Navedo, Cheng, et al., 2010). The dual optical/electrical recording of Ca + influx via LTCC also provides critical information regarding functional regulation of these channels. Importantly, the structurally diverse scaffolding protein AKAP150 was shown to be critical in mediating LTCC regulation. By virtue of its ability to bind PKA, PKC, calcineurin, and the LTCC itself, AKAP150 facilitates LTCC regulation by these kinases and phosphatase (Navedo, Amberg, Nieves, Molkentin, & Santana, 2006; Navedo et al., 2008; Navedo & Santana, 2013; Navedo, Takeda, et al., 2010; Santana & Navedo, 2009). High activity LTCC sparklets were shown to require distinct PKC and calcineurin activity. Accordingly, high activity LTCC sparklets contribute to $[Ca^{2+}]_i$, and myogenic tone during physiological and pathological conditions (Amberg, Navedo, Nieves-Cintrón, Molkentin, & Santana, 2007; Takeda, Nystoriak, Nieves-Cintron, Santana, & Navedo, 2011). Indeed, exacerbated high LTCC sparklet activity that is dependent on PKC or PKA has been linked to increased myogenic tone and activation of prohypertensive signaling pathways in animal models of hypertension and diabetes, respectively (Navedo & Amberg, 2013; Navedo, Takeda, et al., 2010; Nieves-Cintron et al., 2008, 2015; Nystoriak et al., 2014).

In summary, splice variations for the α_{1c}, β, and $\alpha_2\delta$ subunits result in complex functional diversity of LTCCs. As the predominant Ca^{2+} entry pathway in VSM, LTCCs play a key role in modulating VSM contractility and myogenic tone. Thus, mechanisms regulating LTCC subunit composition, posttranslational modifications, and membrane organization have the potential to impact VSM function and vascular reactivity during physiological and pathological conditions.

2.1.2 T-Type Ca^{2+}Channels—TTCCs were first identified as a separate VDCC in guinea pig ventricular myocytes as transient conductance currents of ~8pS with Ba^{2+} as the charge carrier (Catterall, 2011). T-type currents are activated at more hyperpolarized potentials (~ −30 mV). These channels can be blocked by mibefradil, NNC 55-0396, pimozide, penfluridol, and nickel, although caution should be taken as many of these compounds have off-target effects (Gray & Macdonald, 2006). Dihydropyridines such as nifedipine (at nanomolar range) have generally minimal effects on TTCCs. However, it has been shown that nifedipine at micromolar concentrations (>1 μM) can suppress TTCC function (Akaike et al., 1989). The T-type conductance is similar with Ba^{2+} and Ca^{2+} as charge carriers, whereas L-type current is significantly larger in the presence of Ba^{2+} than with Ca^{2+} (Catterall, 2011). So far, no auxiliary β, $\alpha_2\delta$,or γ subunits have been purified for the TTCC. However, some studies suggest that LTCC auxiliary subunits may modulate TTCC functions (Perez-Reyes, 2006).

Several studies have now suggested a role for TTCCs in VSM physiology and vascular reactivity. At the molecular level, transcript and protein for $Ca_V3.1$ and $Ca_V3.2$ have been found in VSM from several vascular beds and in different species, including humans (Abd El-Rahman et al., 2013; Harraz, Abd El-Rahman, et al., 2014; Harraz, Visser, et al., 2015; Kuo, Ellis, Seymour, Sandow, & Hill, 2010). Studies on rat mesenteric arterioles indicate that TTCCs also contribute to vasoconstrictor responses (Gustafsson, Andreasen, Salomonsson, Jensen, & Holstein-Rathlou, 2001; Jensen, Salomonsson, Jensen, & Holstein-Rathlou, 2004). In skeletal muscle arteries, $Ca_V3.1$ and $Ca_V3.2$ are actively involved in maintenance of myogenic tone (VanBavel, Sorop, Andreasen, Pfaffendorf, & Jensen, 2002). In arteriolar SM from the retina, $Ca_V3.1$ activity has been reported, indicating a potentially important role in retinal microcirculation (Fernandez, McGahon, McGeown, & Curtis, 2015).

$Ca_V3.1$ and $Ca_V3.2$ channels have also been identified in rat and mouse cerebral VSM as the nifedipine-insensitive component of Ba^{2+} currents (Abd El-Rahman et al., 2013; Harraz, Abd El-Rahman, et al., 2014; Harraz, Visser, et al., 2015; Kuo et al., 2010; Nikitina et al., 2006). Interestingly, $Ca_V3.1$ seems to be replaced by $Ca_V3.3$ in human cells (Harraz, Visser, et al., 2015). $Ca_V3.1$/$Ca_V3.3$ and $Ca_V3.2$ contributions to the observed T-type current in these cells could be distinguished based on a 20-fold higher sensitivity of $Ca_V3.2$ to blockage by Ni^{2+} ($Ca_V3.2$ EC_{50} = 12 μM; $Ca_V3.1$ EC_{50} = 250 μM) (Lee, Gomora, Cribbs, & Perez-Reyes, 1999). By exploiting this selectivity and the use of genetically modified mice, the contribution of these channels to the regulation of the myogenic response was found to diverge (Fig. 1). Whereas $Ca_V3.1$/$Ca_V3.3$ seems to mediate pressure-induced constriction, $Ca_V3.2$ contributes to negative feedback regulation of pressure-induced tone by modulating the RyR–large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channel axis (Harraz, Abd El-Rahman, et al., 2014; Harraz, Brett, & Welsh, 2014; Harraz, Visser, et al., 2015). Another interesting detail is that TTCCs and LTCCs appear to respond to different intravascular pressures following their voltage dependence (Harraz, Abd El-Rahman, et al., 2014; Harraz, Visser, et al., 2015). Accordingly, $Ca_V3.1$/$Ca_V3.3$ channels predominantly contribute to myogenic tone at lower intraluminal pressures (e.g., 20–40 mmHg), in which membrane potential of VSM is ~ −60 to −50 mV. Conversely, $Ca_V1.2$ function is prominent at more depolarized VSM membrane potentials (~−45 to −36 mV) observed at greater intraluminal pressures (Knot & Nelson, 1998). Regulation of TTCC activity by protein kinases may also contribute to modulate VSM function and the myogenic response. Accordingly, PKA and PKG activation has been shown to inhibit TTCC in VSM (Harraz, Brett, et al., 2014; Harraz & Welsh, 2013a). This TTCC suppression could limit extracellular Ca^{2+} entry, which may contribute to the well-known vasodilatory responses triggered by these kinases. Thus, along with LTCCs, TTCCs may contribute to precise maintenance of myogenic tone through their ability to activate at lower pressures.

2.2 TRP Channels

TRP channels are a superfamily of cationic channels with 28 encoding genes. Based on their sequence homology, these channels can be further categorized into six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPA (ankyrin), and TRPML (mucolipin) (Earley & Brayden, 2015). Sequence analysis suggests that TRP

channels consist of six membrane-spanning helices (S1–S6) with intra-cellular NH_2- and COOH-termini of variable lengths. While a crystal structure has not yet been resolved for any TRP channel, electron cryomicroscopy studies of the capsaicin-activated TRPV1 channel demonstrate four symmetrical subunits with S5 and S6 loop forming the ion pore. The structure also contains a selectivity filter, which is differentially regulated by endogenous and exogenous ligands (Liao, Cao, Julius, & Cheng, 2013). Functional TRP channels consist of four subunits and can be homomeric or heteromeric in nature. As most cells express multiple TRP channel isoforms, it is likely that these channels exist in heteromultimeric form. The NH_2- and COOH-termini have several domains that can modify and regulate channel function. For example, the number of ankyrin repeats on the TRPV1 and TRPA1 channels has been shown to regulate channel activity (Gaudet, 2008). Similarly, the COOH-terminus of some TRP channels contains a CaM/IP_3-binding domain, serine–threonine kinase target sequence, and PDZ protein–protein interaction domains, depending on transcript splicing patterns (Walker, Hume, & Horowitz, 2001).

Multiple TRP channels are expressed in VSM. In these cells, TRP channels contribute to regulation of membrane potential, contraction, and development of myogenic tone (Earley & Brayden, 2015). Additionally, certain TRP channels contribute to vascular mechanosensitivity via G-protein-coupled signaling in resistance arteries (Earley & Brayden, 2015). Almost all TRP channels are permeable to Ca^{2+} with the exception of TRPM4 and TRPM5, which are Ca^{2+} activated, but not Ca^{2+} permeable (Earley & Brayden, 2015). Here, we review key issues on specific vascular TRP channels.

2.2.1 TRPV1—TRPV1 are nonselective cation channels with the preference for Ca^{2+} to Na^+ ions (10:1) (Caterina et al., 1997). TRPV1 channels are primarily expressed in sensory neurons and play a crucial role in heat sensation and nociception (Meents, Neeb, & Reuter, 2010). TRPV1 can be endogenously activated by acidic pH < 5.5 and derivatives of arachidonic acid, and exogenously by capsaicin and resiniferatoxin. Furthermore, channel activity and trafficking are regulated by PKA and PKC (Efendiev, Bavencoffe, Hu, Zhu, & Dessauer, 2013; Koda et al., 2016) with potential important implications in the regulation of vascular tone (Earley & Brayden, 2015). Activation of these channels in sensory nerves results in release of vasodilatory neuropeptides and consequently, dilation of the blood vessels. In SM, TRPV1 activation elicits contraction. For example, skeletal muscle arterioles exhibit significant constriction in response to application of the TRPV1 activator capsaicin (Toth et al., 2014). TRPV1 expression has also been reported in arterioles from thermoregulatory tissues including dura, cremaster, skin, and ear (Cavanaugh et al., 2011). Yet, TRPV1 expression does not seem to be ubiquitous among vascular tissues (Baylie & Brayden, 2011).

2.2.2 TRPV2—TRPV2 channels have been reported in aortic, mesenteric, and basilar artery VSM (Earley & Brayden, 2015). In aortic myocytes, application of a hypotonic solution resulted in TRPV2 activation, increased Ca^{2+} influx, and constriction (Muraki et al., 2003). Yet, more studies are required to elucidate a functional role for TRPV2 in different vascular beds.

2.2.3 TRPV4—TRPV4 channels have been implicated in regulation of myogenic tone. This channel can be stimulated by mechanical stress, including sheer stress and cell swelling. In cerebral VSM, TRPV4 channels are regulated by PKC and their activation results in Ca^{2+} influx (i.e., TRPV4 sparklets) (Mercado et al., 2014). Unexpectedly, this activation was associated with vasodilation rather than vasoconstriction (Earley, Heppner, Nelson, & Brayden, 2005). Ca^{2+} entry during a single TRPV4 sparklet is ~ 100-fold larger than a $Ca_V1.2$ sparklet (Mercado et al., 2014). This highly localized TRPV4 sparklet may stimulate the activity of RyR in the SR resulting in generation of Ca^{2+} sparks. The ensuing Ca^{2+} sparks activate BK_{Ca} channels leading to VSM membrane potential hyperpolarization and vasorelaxation (Fig. 1) (Earley et al., 2005, 2009). An intriguing possibility, based on the large and localized flux of Ca^{2+} through TRPV4, is that these channels could also directly activate nearby BK_{Ca} channels to regulate vascular reactivity. This hypothesis requires examination.

2.2.4 TRPC1—TRPC1 channels form functional heteromers with TRPC4 and/or TRPC5, which can be regulated by G_q-coupled signaling pathways (Sabourin et al., 2009; Strubing, Krapivinsky, Krapivinsky, & Clapham, 2001). The functional relevance of TRPC1 channels in VSM, however, is controversial. For instance, studies support (Bergdahl et al., 2003, 2005; Inoue et al., 2006)and refute (DeHaven et al., 2009; Dietrich et al., 2007; Varga-Szabo et al., 2008) a role for TRPC1 in store-operated Ca^{2+} entry (SOCE) in VSM. Moreover, Ca^{2+} influx via TRPC1 has been associated with BK_{Ca} channel activation and VSM relaxation (Kwan et al., 2009). This is somewhat paradoxical as a recent study suggested that (1) TRPC1 does not form functional homomeric channels and (2) TRPC1-containing heteromers exhibit decreased Ca^{2+} permeability (Storch et al., 2012). More research is necessary to define the mechanisms by which TRPC1 modulates BK_{Ca} channel activity and vascular reactivity.

2.2.5 TRPC3—TRPC3 in VSM has been linked to vascular tone regulation via stimulation of a variety of G-protein-coupled receptors (GPCRs) including ANG II and endothelin-1 (ET-1) receptors (Earley & Brayden, 2015). Accordingly, TRPC3 does not seem to have an effect on intrinsic vascular tone, suggesting that TRPC3 may not be essential in pressure-induced tone but rather receptor-mediated vasoconstriction of the arteries (Reading, Earley, Waldron, Welsh, & Brayden, 2005; Xi et al., 2008). Indeed, in cerebral VSM, the mechanism of TRPC3-induced vasoconstriction implicates IP_3 facilitated coupling of IP_3R and TRPC3 (Fig. 1)(Xi et al., 2008). The activation of TRPC3 results in cation influx (e.g., Na^+ and Ca^{2+}) and consequently membrane depolarization leading to opening of LTCCs and vasoconstriction.

2.2.6 TRPC4—A role for TRPC4 in aortic and mesenteric VSM has been suggested (Lindsey & Songu-Mize, 2010). Under prolonged cyclic stretch conditions, TRPC4 expression appears to decrease along with a decrease in SOCE. These studies suggest that downregulation of TRPC4 may be a protective mechanism against stretch-mediated increase in SOCE.

2.2.7 TRPC5—TRPC5 channels have been implicated in SOCE in VSM when coassembled with other TRPC subunits. For example, application of an anti-TRPC5 antibody was found to inhibit SOCE in VSM from cerebral arterioles in response to store depletion (Xu, Boulay, Flemming, & Beech, 2006). Likewise, currents evoked by cyclopiazonic acid (a SERCA pump inhibitor) were inhibited by an anti-TRPC5 antibody (Saleh, Albert, & Large, 2009). Altogether, these results suggest a role for TRPC5 in SOCE in VSM.

2.2.8 TRPC6—TRPC6-mediated Ca^{2+} mobilization in VSM has been associated with regulation of vasoconstriction. TRPC6 channels can be activated via mechanosensation, such as cell swelling and sheer stress, to promote vasoconstriction (Welsh, Morielli, Nelson, & Brayden, 2002). These channels can also be activated by GPCRs (Inoue et al., 2001). For example, application of 1 nM ANG II activates TRPC6 channels via a mechanism that is directly associated with diacylglycerol, and independent of PKC (Helliwell & Large, 1997; Saleh, Albert, Peppiatt, & Large, 2006). More recently, an exciting study proposed that Ca^{2+} entry via TRPC6 plays a critical role as part of a force-sensing complex that bolsters Ca^{2+} release through IP_3Rs on the SR to stimulate TRPM4 channel activity and myogenic tone (Fig. 1)(Gonzales et al., 2014). However, despite the wealth of information on this channel in VSM, additional studies are needed to establish their (1) contributions to local and global Ca^{2+} signals, (2) role in different vascular beds, and (3) mechanisms of activation and mechanosensation.

2.2.9 TRPM4—TRPM4 is one of two TRP channels that are Ca^{2+} activated, but not Ca^{2+} permeable. Nonetheless, TRPM4 channels in VSM play an essential role in development of myogenic tone (Earley, Waldron, & Brayden, 2004; Gonzales et al., 2014; Li & Brayden, 2015). In VSM from rat cerebral arteries, these channels are activated by local IP3R-mediated increases in $[Ca^{2+}]_i$ (Fig. 1)(Gonzales, Amberg, & Earley, 2010). Their activity can be differentially regulated by specific signaling proteins depending on the vascular bed (Earley, Straub, & Brayden, 2007; Li & Brayden, 2015). More recently, RhoA/Rho-associated protein kinase has been demonstrated to potentiate TRPM4 in VSM of parenchymal arterioles (Li & Brayden, 2015). Other TRPM channels, such as TRPM7 and TRPM8, are also expressed in VSM. Whereas TRPM7 has been implicated mainly in Mg^{2+} homeostasis (He, Yao, Savoia, & Touyz, 2005), little is known about the functional role of TRPM8 in VSM.

2.2.10 TRPP2—TRPP are Ca^{2+}-permeable channels known to be mechanosensitive (Earley & Brayden, 2015). Recognized also as polycystic-1 and -2 proteins, TRPP1 and TRPP2 expression has been described in multiple vascular beds, including mesenteric and cerebral arteries (Narayanan et al., 2013; Sharif-Naeini et al., 2009). In these arterial beds, the activation of TRPP1 and TRPP2 seems to regulate the myogenic response, albeit via different mechanisms. TRPP2 activation is also associated with differential regulation of IP_3R and RyR in cells (presumably VSM) from cerebral arteries with important implications for modulation of vascular reactivity (Abdi et al., 2015). Yet, several issues still require further examination such as (1) contribution of TRPP2 to local and global Ca^{2+} signals, (2) how TRPP2 modulates IP_3R and RyR activity, (3) what role, if any, does interaction of

TRPP2 with other ion channels (e.g., TRPP1) have on the control of vascular reactivity, and (4) how TRPP2 may contribute to VSM physiology and pathophysiology.

2.2.11 Intracellular TRP Channels—Accumulating evidence suggests that TRP channels in intracellular membranes may also play a critical role in regulating Ca^{2+} homeostasis and cell function (Dong, Wang, & Xu, 2010). For example, TRPV1 and TRPP2 localized to the endoplasmic reticulum are thought to be involved in intracellular Ca^{2+} regulation (Koulen et al., 2002; Olah et al., 2001). Furthermore, TRPM2 and TRPML may play a role in Ca^{2+} release from lysosomes, which may contribute to oxidative stress of the cell (Dong et al., 2010; Lange et al., 2009). In VSM, TRPM7-containing vesicles are quickly trafficked to the plasmalemma in response to shear stress (Oancea, Wolfe, & Clapham, 2006). This resulted in a significant increase in TRPM7-like currents, which may contribute to increased $[Ca^{2+}]_i$ and impaired VSM function during pathological conditions (Dong et al., 2010). Extensive studies, however, are still required to completely understand the role of intracellular TRP channels in VSM.

2.3 Orai and STIM

Depletion of Ca^{2+} from intracellular stores via activation of plasmalemmal phospholipase C (PLC)-coupled receptors and subsequent IP_3R-mediated Ca^{2+} release triggers Ca^{2+} influx from extracellular sources. This process of SOCE was first introduced as a mechanism of controlled and sustained Ca^{2+} entry following activation of surface membrane receptors (Putney, 1986). The physiological and pathological significance of the Ca^{2+} release-activated Ca^{2+} current (I_{CRAC}) was brought to light by rare cases of severe immunodeficiency in patients with inherited defects in components mediating SOCE that profoundly impairs immune cell function (Picard et al., 2009). A great deal of progress has been made in the field of SOCE and has highlighted an emerging importance of I_{CRAC} in multiple cell types, including VSM. Following decades-long investigations aimed at revealing the molecular identity of I_{CRAC}, the plasmalemmal Ca^{2+}-permeable channels and associated S/ER-localized channel activators responsible for SOCE were only recently identified as Orai and STIM, respectively (Roos et al., 2005; Zhang et al., 2005). It is now recognized that upon reduction of Ca^{2+} concentration in S/ER ($[Ca^{2+}]_{S/ER}$), the $[Ca^{2+}]_{S/ER}$ sensor STIM1 undergoes dynamic spatial reorganization into aggregate clusters that interact with Orail channels in the plasmalemma to facilitate I_{CRAC}. This section will briefly review the current state of knowledge regarding molecular and functional aspects of Orai-channel mediated Ca^{2+} signaling in VSM and its potential contribution to vascular disease states.

The Orai homologues are plasmalemmal ion channels encoded by three genes (i.e., Orai1, Orai2, and Orai3) with little genetic or structural similarity to that of other known Ca^{2+}-permeable channels. In mammals, alternative methionine translation initiation gives rise to two forms of Orai1: a 33 kDa long form (Oria1α) and a 23 kDa short form (Oria1β) (Fukushima, Tomita, Janoshazi, & Putney, 2012). Perhaps as a result of these proteomic and functional differences, Orai1α and Orai1 β could display preference for certain binding partners (e.g., TRPC1 vs Orai3) to exhibit selective participation in distinct Ca^{2+} currents (Desai et al., 2015). Sequence analyses and crystallization studies have revealed that Orai channels are heteromeric structures, with each channel consisting of 4–6 Orai subunits (Hou,

Pedi, Diver, & Long, 2012). Each subunit consists of four highly conserved transmembrane helices (M1–M4). The side chains of amino acids in M1 helices of each Orai subunit form a 55 A pore. The extracellular face of the Orai pore has a distinct ring of glutamate residues that form its selectivity filter (Hou et al., 2012). This feature is thought to render the highly selective nature of I_{CRAC} being almost exclusively carried by Ca^{2+} over Na^+ or K^+ ions (Hoth & Penner, 1993). Each Orai subunit consists of cytosolic NH_2 and COOH-termini, which contain sites for functional regulation by Ca^{2+}/CaM, PKC, and STIM proteins (Frischauf et al., 2009; Hooper et al., 2015; Mullins, Park, Dolmetsch, & Lewis, 2009).

It is now established that Orai channels are activated via physical molecular interaction with the stromal interaction molecules (STIM1 and STIM2), which function as Ca^{2+} sensors within the S/ER (Roos et al., 2005; Zhang et al., 2005). STIM proteins are single-transmembrane proteins that are primarily located in the ER, although small populations of STIM1 that play a role in controlling Ca^{2+} entry have also been observed in the plasmalemma (Spassova et al., 2006). S/ER STIM senses alterations in luminal $[Ca^{2+}]_i$ via NH_2 terminal canonical EF-hand domains. Upon a depletion of S/ER Ca^{2+} and dissociation of Ca^{2+} ions from the NH_2 terminal EF-hand domains, STIM proteins undergo unfolding and aggregation at plasmalemmal-S/ER junctions where they activate Orai channels via direct physical interactions to induce conformational changes in the channel structure. Importantly, proper Orai/STIM communication requires COOH-terminus coiled-coil interaction domains of both Orai and STIM (Frischauf et al., 2009; Muik et al., 2008).

Determining the precise physiological role of the SOCE machinery in cardiovascular tissues has been hampered by a lack of selective pharmacological modulators of Orai channels and STIM proteins. The widely used nonselective cation channel inhibitor 2-aminoethoxydiphenyl borate (2-APB) has been shown to exhibit concentration-dependent and divergent effects on I_{CRAC} (Prakriya & Lewis, 2001). A new class of I_{CRAC} inhibitors was shown to have selective effects on Orai channels independent of STIM oligomerization or STIM/Orai interaction (Derler et al., 2013). For example, in VSM, the I_{CRAC} inhibitor S66 prevented Ca^{2+} influx following store depletion with nanomolar potency (Li et al., 2011). Thus, the emergence of novel compounds that can specifically target Orai–Orai/STIM interactions and STIM aggregation will significantly aid in future studies to investigate I_{CRAC}-related mechanisms in cardiovascular physiology and pathology.

Expression of Orai and STIM ranges from very low to nondetectable in quiescent VSM. Yet, store depletion by thapsigargin and subsequent SOCE was shown to be prominent in synthetic cultured rat aortic smooth muscle, but not in freshly dispersed VSM (Potier et al., 2009). In line with enhanced SOCE in dedifferentiated SM present in many disease states, transformation of contractile VSM to a noncontractile proliferative phenotype in culture is associated with substantial upregulation in the expression of Orai and STIM proteins (Berra-Romani, Mazzocco-Spezzia, Pulina, & Golovina, 2008; Potier et al., 2009). Consistent with in vitro findings, expression for both Orai1 and STIM1 were strongly upregulated in association with SM proliferation following balloon angioplasty-induced carotid injury in rats (Zhang et al., 2011). Lentivirus-mediated knockdown of Orai1 in injured vessels prevented conversion of SM to a proliferative phenotype and mitigated neointima formation, suggesting that Orai1-mediated Ca^{2+} entry may be an important determinant of vascular

remodeling during injury such as in restenosis. Further, in vitro studies have confirmed that SOCE becomes a predominant source of Ca^{2+} influx in synthetic VSM that plays a pivotal role in proliferative and migratory processes. Thus, adaptive changes in Orai and STIM expression and function may drive phenotypic modulation during angiogenesis and vascular repair, as well as in disease.

The precise molecular determinants underlying Orai/STIM up-regulation in phenotypic switching of quiescent to proliferative/migratory SM is still unresolved. A major driving factor of phenotypic switching of VSM is the polypeptide platelet-derived growth factor (PDGF). PDGF, via activation of the PDGFβ receptor and downstream PLCγ-mediated SR Ca^{2+} release, is an important activator of Orai1 channels in SM. Whether STIM-independent regulation of Orai occurring downstream of PDGF stimulation significantly contributes to Ca^{2+} influx in proliferating/migratory VSM is still unclear. However, in addition to the well-known role in activation of Orai channels, STIM1 clustered in ER/PM junctions also inhibits Ca^{2+} influx through $Ca_V1.2$ channels and leads to internalization of LTCC (Park, Shcheglovitov, & Dolmetsch, 2010; Wang et al., 2010). This mechanism, however, could not be confirmed in quiescent VSM (Takeda et al., 2011), perhaps reflecting distinct roles for STIM proteins in proliferative vs contractile cells.

It is also important to mention the role that Orai channels play in store-independent, ligand-activated Ca^{2+} entry in SM that is mediated by Orai1, Orai3, and STIM1. This nonstore-operated strongly inwardly rectifying current, termed I_{ARC}, is gated by arachidonic acid and its metabolite leukotriene C4 (Zhang et al., 2015). In VSM, Ca^{2+} entry requiring Orai1, Orai3, and STIM1 has been observed independent of sustained store depletion following application of the proinflammatory peptide thrombin. Like Orai1 and STIM1, Orai3 protein was also upregulated in an experimental model of carotid artery injury and in vivo knockdown of this subunit alone, blunted neointima formation. These findings suggest that heteromultimerization of Orai channels could give rise to store-dependent and store-independent Ca^{2+} entry pathways that could contribute to maintenance of the synthetic VSM phenotype in several disease states.

3. SR Ca^{2+} CHANNELS

Ca^{2+} release channels located on the SR membrane of VSM play pivotal roles in controlling cell excitability and vascular reactivity. The two major classes of Ca^{2+} release channels in VSM are RyR and IP_3R. In the following section, we describe their role in VSM.

3.1 Ryanodine Receptors

RyRs are intracellular Ca^{2+} channels that mediate Ca^{2+} release from the SR. Three RyR isoforms (RyR1–RyR3) encoded by three distinct genes have been identified (Lanner, Georgiou, Joshi, & Hamilton, 2010). Structural models predicted both NH_2- and COOH-termini to be cytosolic and the pore to have 4–12 membrane-spanning domains (Lanner et al., 2010). Single-particle electron cryomicroscopy studies have provided insights into channel gating and interaction with modulators (Samso, Wagenknecht, & Allen, 2005; Serysheva et al., 2008). Recently, 4.8 and 6.8 A resolution structures of the RyR were described by two independent groups (Efremov, Leitner, Aebersold, & Raunser, 2015; Zalk

et al., 2015). Both reports suggest that Ca^{2+} sensitivity of RyR1 is imparted by EF-hand domains in α-solenoid structures that connect the cytoplasmic region to the channel pore.

mRNA transcript and protein levels have been detected for all RyR isoforms in VSM. RyR1 and RyR2 mediate Ca^{2+} sparks (e.g., Ca^{2+} release from intracellular stores through RyRs) in portal vein SM (Coussin, Macrez, Morel, & Mironneau, 2000), whereas RyR2 has been found to be the predominant isoform in VSM from rat resistance vessels (Vaithianathan et al., 2010). Several studies suggest that in contrast to the tight coupling between LTCCs and RyRs in skeletal and cardiac muscle, a loose coupling mechanism may exist in VSM in which LTCCs indirectly modulate RyRs by contributing to global $[Ca^{2+}]_i$ and SR Ca^{2+} load (Collier, Ji, Wang, & Kotlikoff, 2000; Essin et al., 2007). Interestingly, recent studies demonstrate that application of Ni^{2+} at a concentration that selectively inhibits $Ca_V3.2$ reduced Ca^{2+} spark activity in VSM from WT mice, but had no effect in cells from $Ca_V3.2$ knockout mice (Harraz, Brett, et al., 2015). Consistent with a role for $Ca_V3.2$ in modulation of Ca^{2+} sparks, these channels were found juxtaposed with RyR in specific microdomains (Harraz, Abd El-Rahman, et al., 2014), suggesting that Ca^{2+} influx through TTCCs may contribute to RyR activation in VSM (Fig. 1). This may represent a novel mechanism for regulation of RyRs, VSM excitability, and vascular reactivity that requires further examination.

In VSM, RyR can be activated by caffeine, and depending on its concentration, it can induce massive Ca^{2+} release from intracellular stores or increase the frequency of Ca^{2+} sparks (Jaggar, Porter, Lederer, & Nelson, 2000). The receptor can be inhibited in a concentration-dependent manner by the alkaloid ryanodine. Accordingly, at low concentrations, ryanodine can activate RyR, while at higher concentrations, it inhibits the receptor. Other pharmacological agents such as tetracaine have been used to block RyR and examine their role in VSM function. However, their use is limited due to nonspecific effects. RyRs play a central role in excitation–contraction coupling in both skeletal and cardiac muscle where they contribute to the global increase in $[Ca^{2+}]_i$ necessary for contraction. However, RyRs influence VSM excitability indirectly by modulating the activity of plasmalemma ion channels (Fig. 1). In a landmark study, it was found that Ca^{2+} sparks could simultaneously activate multiple BK_{Ca} channels in the plasmalemma to produce spontaneous transient outward currents (STOCs) and promote hyperpolarization and relaxation of VSM in small resistance arteries (Nelson et al., 1995; Perez, Bonev, Patlak, & Nelson, 1999). The spatial proximity between the plasmalemma and the SR in VSM (Somlyo, 1985) permits Ca^{2+}sparks to activate BK_{Ca} channels with minimal effects on global $[Ca^{2+}]_i$. In rabbit portal vein, however, RyRs have been found to depolarize VSM through activation of Ca^{2+} sensitive chloride channels (Saleh & Greenwood, 2005; Wang, Hogg, & Large, 1992). This highlights the importance of RyR in fine-tuning VSM excitability among different vascular beds.

Regulation of the functional coupling between RyR and BK_{Ca} channels has profound implications for VSM function. For instance, the vasodilatory effects of nitric oxide and forskolin can be attributed, at least in part, to an increase in PKG and PKA activity that acts on RyR to stimulate Ca^{2+} sparks-mediated STOC frequency (Jaggar et al., 2000). Conversely, activators of PKC inhibit RyR activity, which reduces STOC frequency and

could contribute to vasoconstriction (Amberg et al., 2007; Bonev, Jaggar, Rubart, & Nelson, 1997). In addition, any disturbance on BK_{Ca} channel Ca^{2+} sensitivity may impact functional RyR–BK_{Ca} coupling, and vascular contractility; a point well illustrated in animal models of hypertension. In these animals, decreased expression of BK_{Ca} channel β1 subunit reduces BK_{Ca} Ca^{2+} sensitivity resulting in impaired STOC activity, increased myogenic tone, and hypertension (Amberg, Bonev, Rossow, Nelson, & Santana, 2003; Nieves-Cintron, Amberg, Nichols, Molkentin, & Santana, 2007). The coupling strength between RyR and BKCa channel is also affected in animal models of diabetes (Nystoriak et al., 2014). These examples highlight the relevance of the relationship between RyR and BK_{Ca} channels in VSM with impaired communication leading to vascular dysfunction.

3.2 Inositol-1,4,5,-Trisphosphate Receptors

IP_3R is a ubiquitously expressed Ca^{2+} release channel localized to the SR membrane (Narayanan et al., 2012; Nixon, Mignery, & Somlyo, 1994). These channels consist of four membrane-spanning subunits surrounding the central ion permeation pore. Each subunit contains six transmembrane domains, a luminal loop that forms the ion-conducting pore between transmembrane domains 5 and 6, and cytosolic NH_2- and COOH-termini. The NH_2-terminus is further subdivided into a suppression domain that inhibits IP_3 binding, an IP_3-binding core domain, binding sites for ATP and Ca^{2+}, and a coupling domain for physical interactions with TRPC channels. The COOH-terminus seems to contribute to IP_3R tetramerization, and recent electron cryomicroscopy studies with a resolved IP_3R structure at 4.7 Å implicated this domain in channel gating (Fan et al., 2015). Moreover, these studies also suggest that the gate for the Ca^{2+} conduction path includes several hydrophobic residues located closer to the cytosolic side of the SR membrane (Fan et al., 2015). Yet, further experiments will be needed to completely understand the permeation, gating, and regulatory mechanisms governing IP_3R function.

Three different isoforms of IP_3R (IP_3R1, IP_3R2, IP_3R3) have been reported (Narayanan et al., 2012). While expression of all three isoforms has been found in VSM from aorta, mesenteric, and cerebral arteries, IP_3R1 seems to be the predominant isoform in VSM from small resistance arteries (Grayson, Haddock, Murray, Wojcikiewicz, & Hill, 2004; Zhao, Adebiyi, Blaskova, Xi, & Jaggar, 2008; Zhou et al., 2008). Yet, the expression profile of the IP_3R isoforms can vary depending on the developmental stage. Accordingly, expression of IP_3R3 is high in neonatal SM, decreases during development, and is surpassed by increasing IP_3R1 expression in adult SM (Tasker, Michelangeli, & Nixon, 1999). High levels of IP_3R2 and IP_3R3 expression have also been found in proliferating SM (Tasker, Taylor, & Nixon, 2000). These IP_3R isoforms also differ in IP_3-binding affinities as follows: $IP_3R2 > IP_3R1 > IP_3R3$ (Newton, Mignery, & Sudhof, 1994; Wojcikiewicz & Luo, 1998). Physical localization of IP_3R on the SR membrane is also isoform and tissue-dependent, which may be important for distinct physiological functions such as gene expression and VSM excitability (Nixon et al., 1994; Tasker et al., 2000; Zhao et al., 2008).

IP_3R activation is stimulated by the second messenger IP_3, which results from the hydrolysis of phosphatidylinositol 4,5-bisphosphate by PLC in response to activation of Gq/11-coupled receptors. Indeed, IP3R activity in VSM can be stimulated by many endogenous vasoactive

molecules that act through Gq/11-coupled receptors to produce IP3, including ET-1, acetylcholine, noradrenaline, and serotonin (Berridge, 2008). Pharmacological inhibition of IP_3R can be achieved with the application of widely used agents such as 2-APB and xestospongin C. IP_3R inhibition may have distinct effects on vascular reactivity. For instance, in mouse mesenteric arteries, IP_3R inhibition with xestospongin C did not affect the myogenic tone, but did prevent the phenylephrine-induced vasoconstriction (Mauban, Zacharia, Fairfax, & Wier, 2015). IP_3R activity in VSM can be modulated by $[Ca^{2+}]_i$, luminal SR Ca^{2+} load, ATP, several protein kinases (e.g., PKA, PKG), regulatory proteins (e.g., RACK, FKBP12), reactive oxygen species (ROS), and pH (Bezprozvanny, Watras, & Ehrlich, 1991; Iino, 1990; Narayanan et al., 2012).

The activation of IP_3R can produce multiple Ca^{2+} signals, including Ca^{2+} puffs and Ca^{2+} waves, with important implications for VSM function. Ca^{2+} puffs are elementary, localized Ca^{2+} release events produced by clusters of IP_3R(Parker & Smith, 2010; Tovey et al., 2001). Ca^{2+} puffs have been observed in colonic and ureteric SM (Boittin et al., 2000; Olson, Chalmers, & McCarron, 2010), but not in VSM, perhaps due to differences in IP_3R localization, distribution, and function. Yet, recent indirect evidence suggests that Ca^{2+} puffs could alter cerebral VSM function through modulation of plasmalemmal ion channel activity. Accordingly, localized Ca^{2+} release via IP_3R was shown to promote the opening of TRPM4 channels leading to pressure-induced membrane depolarization and cell contraction (Fig. 1)(Gonzales et al., 2010; Gonzales & Earley, 2012).

On the other hand, Ca^{2+} waves are propagating elevations in $[Ca^{2+}]_i$ resulting from Ca^{2+} release via IP_3R, RyR, or both due to electrical, mechanical, and receptor-mediated stimulation in VSM (Amberg & Navedo, 2013; Narayanan et al., 2012; Wray & Burdyga, 2010). The contributions of IP_3R and/or RyR to spontaneous and agonist-induced Ca^{2+} wave generation seem to differ in VSM according to the vascular bed (Fig. 1) (Boittin, Macrez, Halet, & Mironneau, 1999; Dabertrand, Nelson, & Brayden, 2012; Gordienko & Bolton, 2002; Jaggar, 2001; Wray & Burdyga, 2010; Zacharia, Zhang, & Wier, 2007; Zhao et al., 2008). For example, RyR but not IP_3R was found to play a prominent role in spontaneous Ca^{2+} wave generation and propagation in cerebral VSM (Jaggar, 2001; Jaggar & Nelson, 2000), whereas both RyR and IP_3R appear to be involved in Ca^{2+} waves in portal vein SM (Gordienko & Bolton, 2002). Conversely, IP_3Rs are involved in agonist-induced Ca^{2+} waves, which may propagate with involvement of RyR activation perhaps via a Ca^{2+}-induced Ca^{2+} release (CICR) mechanism (Boittin et al., 1999; Gordienko & Bolton, 2002; Wray & Burdyga, 2010; Zhao et al., 2008). The mechanisms of wave propagation, however, remain unclear. Future studies should comprehensively investigate the levels of RyR and IP_3R expression, subcellular distribution and activation, their regulation by cytosolic and SR Ca^{2+} concentration, as well as variations in these properties in VSM among different vascular beds.

IP_3R-mediated SR Ca^{2+} release-dependent and -independent mechanisms have been described to regulate VSM function. IP_3R-mediated Ca^{2+} waves have been suggested to contribute to agonist-induced VSM contraction and the myogenic response (Boittin et al., 1999; Lamont & Wier, 2004; Zacharia et al., 2007; Zhao et al., 2008). This response seems to involve an increase in the frequency of Ca^{2+} waves that could contribute, at least in part,

to elevate global $[Ca^{2+}]_i$ to activate the contractile machinery (Hill-Eubanks, Werner, Heppner, & Nelson, 2011). Interestingly, recent studies have also revealed a significant contribution for IP_3R to VSM excitability that is independent of its ability to mediate SR Ca^{2+} release. At physiological intravascular pressures, PLC-coupled receptors promote vasoconstriction by activating a cation current (I_{Cat}) that requires physical coupling between TRPC3 and IP_3R(Adebiyi et al., 2010; Xi et al., 2008; Zhao et al., 2008).

IP_3R-mediated Ca^{2+} waves have also been proposed to contribute to pressure-induced vasoconstriction, at least at low intravascular pressures, in cerebral VSM (Adebiyi et al., 2010; Gonzales et al., 2014; Mufti et al., 2010; Xi et al., 2008). Two recent studies proposed a role for PLCγ1 in this process, albeit via distinct signaling pathways. One study implicates pressure-induced stimulation of PLCγ1 activity to TRPC6-mediated Ca^{2+} influx leading to activation (via CICR) of IP_3-sensitized IP_3R. The resulting localized rise in $[Ca^{2+}]_i$ activates neighboring TRPM4 channels to depolarize VSM and contribute to development of the myogenic response (Gonzales et al., 2014). A second study suggested the involvement of integrin $\alpha_v\beta_3$ in activation PLCγ1, IP_3 production, IP_3R activation, and Ca^{2+} waves generation in response to an increase in intravascular pressure (Mufti et al., 2015). The ensuing Ca^{2+} waves facilitate MLC_{20} phosphorylation and development of myogenic tone. In principle, these two IP_3R-mediated SR Ca^{2+} release-dependent mechanisms could synergize to contribute to the regulation of pressure-induced vasoconstriction. Future studies should be designed to test this possibility. Additionally, a somewhat counterintuitive role for IP_3,IP_3R, and IP_3R-mediated SR Ca^{2+} release on activation of BK_{Ca} channels in cerebral VSM has been described. IP_3R activation was found to increase BK_{Ca} Ca^{2+} sensitivity (Zhao et al., 2010). This was suggested to facilitate BK_{Ca} channel activity in response to IP_3R-mediated SR Ca^{2+} release to ameliorate agonist-induced vasoconstriction. Thus, multiple IP_3R-mediated SR Ca^{2+} release-dependent and -independent mechanisms can converge to regulate VSM function.

Proliferation of VSM seems to depend on IP_3R-mediated Ca^{2+} release, specifically increased frequency of Ca^{2+} waves (Wilkerson, Heppner, Bonev, & Nelson, 2006). Accordingly, suppression of IP_3R1 expression in A7r5 cell line prevented them from proliferating (Y. Wang et al., 2001). Furthermore, it was found that IP_3R-mediated Ca^{2+} waves are necessary for the dedifferentiation of native VSM from the contractile to proliferative state (Wilkerson et al., 2006), although the mechanisms require further examination.

IP3R-mediated signaling has been proposed to contribute to vascular pathology. For example, mesenteric VSM of ANG II-induced hypertensive mice and spontaneously hypertensive rats display elevated mRNA and protein levels of IP_3R1 (Abou-Saleh et al., 2013). This increased expression was associated with sensitization of IP_3R-mediated Ca^{2+} release, resulting in augmented vasoconstriction in response to stimulation by vasoactive agents in ANG II-induced hypertensive mice. A different study found that increased TRPC3 expression and coupling between TRPC3 and IP3R, but no changes in IP_3R expression, contributed to agonist-induced vasoconstriction during hypertension, and that this did not require IP_3R-mediated SR Ca^{2+} release (Adebiyi et al., 2012). Some of the disparities can be related to the use of different animal models of hypertension, evaluation of different

proteins, and/or diverse experimental conditions and approaches. Impaired IP_3R expression, function, and IP_3R-mediated Ca^{2+} signals in VSM have also been documented to contribute to vascular dysfunction during diabetes and atherosclerosis (Massaeli, Austria, & Pierce, 1999; Searls, Loganathan, Smirnova, & Stehno-Bittel, 2010). Thus, IP_3R-mediated SR Ca^{2+} release-dependent and -independent mechanisms may also contribute to impaired VSM function during pathological conditions.

4. MITOCHONDRIAL Ca^{2+} CHANNELS

Intracellular organelles like mitochondria are emerging as important players in smooth muscle Ca^{2+} handling. Mitochondria harbor various Ca^{2+} channels executing mitochondrial Ca^{2+} turnover. Mitochondrial-calcium-uniporter (MCU), mitochondrial RyR, mitochondrial-Ca^{2+}-channel type-2, rapid mode of uptake, and $H+/Ca^{2+}$ exchanger (Letm1) play a major role in mitochondrial Ca^{2+} influx. The notable channels for mitochondrial Ca^{2+} extrusion include mitochondrial Na^+/Ca^{2+} exchanger, mitochondrial permeability transition pores (mPTPs), and Letm1 (which works as an efflux channel at high mitochondrial Ca^{2+} concentrations ($[Ca^{2+}]_{mito}$)) (Hoppe, 2010). These mitochondrial Ca^{2+} channels may play a physiologically relevant role in VSM, yet they are understudied. In fact, many recent studies centered on the role of the MCU in VSM contractility (McCarron et al., 2013).

In VSM, the mitochondria appear to be a relatively immobile organelle, localized in crucial intracellular regions to operate optimally (McCarron et al., 2013). They sequester cytosolic Ca^{2+} over a wide concentration range (200 nM—10 μM) through the highly Ca^{2+}-selective channel MCU. Mitochondrial Ca^{2+} buffering capacity lies in the substantial amount of phosphate inside the organelle and the electrochemical gradient created by expulsion of H^+ by electron transport chain complexes (McCarron et al., 2013). For instance, mitochondria localized to subplasmalemmal regions of VSM have been shown to buffer stretch-induced cytosolic Ca^{2+} elevation, thereby contributing to intracellular Ca^{2+} homeostasis (Gilbert, Ducret, Marthan, Savineau, & Quignard, 2014). Additionally, evidence suggests that mitochondria do not readily buffer the initial stage of Ca^{2+} influx through LTCC, but rather affect the declining phase of the LTCC-mediated Ca^{2+} signal. However, the organelle is far quicker to scavenge the Ca^{2+} release into the cytosol through IP_3R, thereby targeting the rising phase of Ca^{2+} transient produced by these receptors. Such buffering action may prevent Ca^{2+}-dependent deactivation of IP_3R in VSM, thereby allowing repeated occurrence of IP_3R-mediated Ca^{2+} oscillation and Ca^{2+} waves (McCarron et al., 2013). The cue to distinguish the mitochondrial buffering effect on LTCC Ca^{2+} signals vs IP_3R Ca^{2+} signals may lie in a seminal work in neurons that highlights the differential Ca^{2+} sequestering effect of mitochondria on Ca_V1 and Ca_V2channels solely based on the positional/spatial aspect of the organelle with respect to the ion channel (Wheeler et al., 2012). Interestingly, Ca^{2+} uptake by mitochondria does not affect the ATP production by the organelle (Chalmers & McCarron, 2008).

Mitochondria can also regulate VSM function via its production of ROS and modulation of the activity of several ion channels. For example, Ca^{2+} intake by mitochondria residing at close proximity of the IP_3R causes depolarization of the organelle through an elevation in $[Ca^{2+}]_{mito}$, thereby culminating in increased production of ROS and NF-kB activation

(Narayanan, Xi, Pfeffer, & Jaggar, 2010). NF-kB being a transcription modulator may regulate the expression of LTCC, thus influencing arterial contraction (Narayanan et al., 2010). Recent studies have also demonstrated that the vasoconstrictor ANG II couples with NADPH oxidase to produce discrete microdomains of ROS signaling (Amberg, Earley, & Glapa, 2010). These microdomains can be amplified by adjacent mitochondrial ROS-induced ROS release to promote oxidative activation of PKC resulting in local stimulation of LTCC activity, enhanced Ca^{2+} influx and vasoconstriction (Chaplin, Nieves-Cintron, Fresquez, Navedo, & Amberg, 2015). Notably, disruption of this pathway in vivo ameliorates vascular dysfunction associated with hypertension (Chaplin et al., 2015). Mitochondria-derived ROS can also modulate the activity of RyR and BK_{Ca} channels in VSM and therefore may contribute to vasodilation under certain conditions (Cheranov & Jaggar, 2004; Xi, Cheranov, &Jaggar, 2005). Thus, mitochondria can distinctly regulate VSM function. Future studies should further examine the expression, localization, and function of mitochondrial Ca^{2+} channels, as well as their interplay with other ion channels in modulating cellular Ca^{2+} signals and VSM function.

5. CONCLUSION

Intracellular Ca^{2+} VSM is controlled by an exquisite repertoire of Ca^{2+}-permeable channels to regulate cell excitability, vessel diameter, and ultimately, blood flow. Here, we have discussed our current understanding of the expression, structure, localization, regulation, and functional role of major Ca^{2+}-permeable channels in VSM. Altered regulation of these Ca^{2+}-permeable channels can have profound impact on cardiovascular physiology and pathology. Further research is still required to completely appreciate how all these Ca^{2+}-permeable channels contribute to Ca^{2+} handling, VSM excitability, and vascular reactivity. This can be accomplished with the employment of new, emerging technologies. For instance, the development of innovative imaging tools has made possible the recording of sub-cellular Ca^{2+} signals produced by a single or clusters of Ca^{2+}-permeable channels. As the superior spatiotemporal resolution afforded by these technologies has begun to refine our understanding of Ca^{2+} signaling, such technologies could be adapted to further examine elementary signals produced by distinct Ca^{2+}-permeable channels expressed in VSM. It is increasingly apparent that there is an intricate physical and functional relationship among many of these Ca^{2+}-permeable channels as well as with other ion channels and regulatory signaling proteins. Therefore, more comprehensive knowledge of the cellular distribution of these channels with interacting partners is required. The advent of super-resolution nanoscopy as well as proximity ligation assay technology should aid in this task. It will also be important to systematically examine sex- and tissue-specific variations in the expression, localization, regulation, functional role, and physiological significance of all Ca^{2+}-permeable channels in VSM. Finally, the role of Ca^{2+}-permeable channels in VSM from native human tissue should be examined. This translational approach may confirm mechanisms observed in animal models and, perhaps more importantly, may reveal new information regarding ion channel physiology and pharmacology specific to humans.

Acknowledgments

This work was supported by grants from the National Institute of Health R01-HL098200 (M.F.N.), R01-HL121059 (M.F.N.), R01-HL095870 (L.F.S.), and T32-HL086350 (A.U.S. and M.A.N.) and American Heart Association 14GRNT18730054 (M.F.N.) and 16SDG27260070 (M.A.N.).

ABBREVIATIONS

ANG II	angiotensin II
2-APB	2-aminoethoxydiphenyl borate
BK_{Ca}	large-conductance Ca^{2+}-activated potassium channel
Ca^{2+}	calcium
$[Ca^{2+}]_i$	intracellular Ca^{2+} concentration
$[Ca^{2+}]_{mito}$	mitochondrial Ca^{2+} concentration
CaM	calmodulin
ET-1	endothelin-1
GPCR	G-protein-coupled receptor
IP3R	inositol-1,4,5,-trisphosphate receptor
LTCC	L-type $Ca_V1.2$ channel
PKA	protein kinase A
PKC	protein kinase C
PKG	protein kinase G
PLC	phospholipase C
ROS	reactive oxygen species
RyR	ryanodine receptor
SM	smooth muscle
SOCE	store-operated Ca^{2+} entry
SR	sarcoplasmic reticulum
STOC	spontaneous transient outward current
TRP	transient receptor potential
TTCC	T-type Ca^{2+} channel
VDCC	voltage-dependent Ca^{2+} channel
VSM	vascular smooth muscle cells

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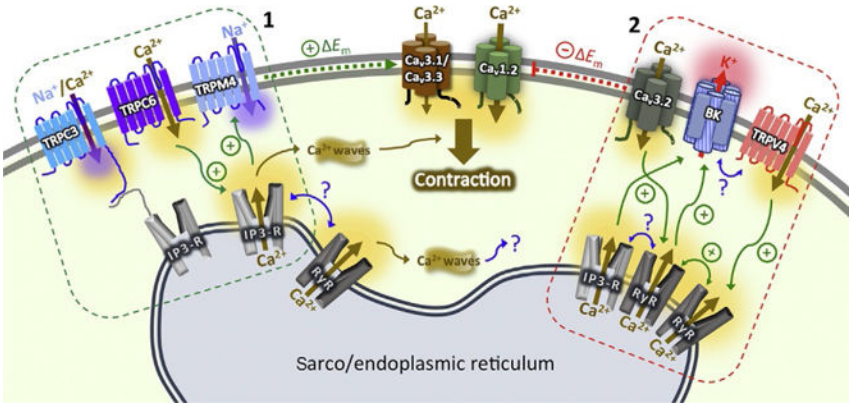

Fig. 1.

Schematic representation of the interplay of major Ca^{2+}-permeable channels involved in the regulation of VSM $[Ca^{2+}]_i$ and contractility. Ca^{2+} influx predominantly through L-type $Ca_V1.2$ and to some extent T-type $Ca_V3.1/3.3$ channels promotes VSM contraction. L-type CaV1.2 and T-type $Ca_V3.1/3.3$ channel activity can be regulated, via membrane potential, by several Ca^{2+}-permeable channels serving (1) depolarizing and (2) hyperpolarizing roles, thus modulating the contractile state of VSM. The emerging role of mitochondria Ca^{2+} channels in regulation of VSM Ca^{2+} homeostasis and vascular reactivity is not depicted in this cartoon for simplicity. (+) denotes positive modulation, (−) represents negative modulation, and (?) indicates areas of uncertainty in the pathway.