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Calcium Channels in Vascular Smooth Muscle

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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 ($[\text{Ca}^{2+}]_i$) 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 $[\text{Ca}^{2+}]_i$. In this review, we discuss the major Ca^{2+} -permeable channels expressed in VSM and their contribution to vascular physiology and pathology.

ABBREVIATIONS

ANG II angiotensin II

2-APB 2-aminoethoxydiphenyl borate

BK_{Ca} large-conductance Ca^{2+} -activated potassium channel

Ca^{2+} calcium

[Ca²⁺]_i intracellular Ca²⁺ concentration
[Ca²⁺]_{mito} mitochondrial Ca²⁺ 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 Ca²⁺ entry
SR sarcoplasmic reticulum
STOC spontaneous transient outward current
TRP transient receptor potential
TTCC T-type Ca²⁺ channel
VDCC voltage-dependent Ca²⁺ channel
VSM vascular smooth muscle cells

1. INTRODUCTION

Highly coordinated control of VSM excitability is essential for proper vascular function and regulation of blood flow. Intracellular Ca²⁺ plays a pivotal role in this process. Accordingly, well-orchestrated and distinct signaling pathways allow tight regulation of [Ca²⁺]_i, which, together with differential Ca²⁺ sensitivity of the contractile machinery, provide additional fine-tuning of VSM contractility. Studies over the last several decades have revealed the expression of multiple Ca²⁺-permeable channels in VSM that coordinate a dynamic and precise control of [Ca²⁺]_i, thereby playing a pivotal role in VSM physiology (Fig. 1). Changes in [Ca²⁺]_i are produced by Ca²⁺ influx through voltage-dependent and -independent plasmalemmal Ca²⁺-permeable channels, as well as Ca²⁺ release from intracellular stores. L-type Ca_v1.2 channels (LTCCs) have long been considered the primary route of Ca²⁺ entry in VSM. Indeed, Ca²⁺ 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 Ca²⁺ channels (TTCCs) are emerging as important

Fig. 1 Schematic representation of the interplay of major Ca^{2+} -permeable channels involved in the regulation of VSM $[\text{Ca}^{2+}]_i$ and contractility. Ca^{2+} influx predominantly through L-type $\text{Ca}_v1.2$ and to some extent T-type $\text{Ca}_v3.1/3.3$ channels promotes VSM contraction. L-type $\text{Ca}_v1.2$ and T-type $\text{Ca}_v3.1/3.3$ 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.

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 $[\text{Ca}^{2+}]_i$ and VSM excitability. RyRs and IP_3Rs are also 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, Adebisi, & 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 $[\text{Ca}^{2+}]_i$ in VSM.

2.1.1 L-Type $\text{Ca}_v1.2$ Channels

LTCCs form the fulcrum in Ca^{2+} dynamics of VSM. 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 (Bezannilla, 2008).

The α_{1c} transcript undergoes extensive alternative splicing, 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 subunits, 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 ($\alpha_2\delta 1$ – $\alpha_2\delta 3$). 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 $\alpha_2\delta 1$ knockdown (Bannister et al., 2009). Furthermore, increased $\alpha_2\delta 1$ 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 $\alpha_2\delta 1$ and $\beta 3$ expression enhances LTCC expression and function, thus contributing to augmented vasoconstriction during hypertension. Therefore, targeting the $\alpha_2\delta 1$ and $\beta 3$ 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} (Arikath & 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 extracellular 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-Cintrón, 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-Cintrón, 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-Cintrón 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-Cintrón, & 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^{2+} 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-Cintrón, 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-Cintrón 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 ~ 8 pS 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 ($>1 \mu M$) 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 $\text{Ca}_v3.1$ and $\text{Ca}_v3.2$ 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, Andreassen, Salomonsson, Jensen, & Holstein-Rathlou, 2001; Jensen, Salomonsson, Jensen, & Holstein-Rathlou, 2004). In skeletal muscle arteries, $\text{Ca}_v3.1$ and $\text{Ca}_v3.2$ are actively involved in maintenance of myogenic tone (VanBavel, Sorop, Andreassen, Pfaffendorf, & Jensen, 2002). In arteriolar SM from the retina, $\text{Ca}_v3.1$ activity has been reported, indicating a potentially important role in retinal microcirculation (Fernandez, McGahon, McGeown, & Curtis, 2015).

$\text{Ca}_v3.1$ and $\text{Ca}_v3.2$ 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, $\text{Ca}_v3.1$ seems to be replaced by $\text{Ca}_v3.3$ in human cells (Harraz, Visser, et al., 2015). $\text{Ca}_v3.1/\text{Ca}_v3.3$ and $\text{Ca}_v3.2$ contributions to the observed T-type current in these cells could be distinguished based on a 20-fold higher sensitivity of $\text{Ca}_v3.2$ to blockage by Ni^{2+} ($\text{Ca}_v3.2$ $\text{EC}_{50} = 12 \mu\text{M}$; $\text{Ca}_v3.1$ $\text{EC}_{50} = 250 \mu\text{M}$) (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 $\text{Ca}_v3.1/\text{Ca}_v3.3$ seems to mediate pressure-induced constriction, $\text{Ca}_v3.2$ 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, $\text{Ca}_v3.1/\text{Ca}_v3.3$ 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, $\text{Ca}_v1.2$ 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 intracellular 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 $\text{pH} < 5.5$ 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 shear 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 $\text{Ca}_v1.2$ 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 shear 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 IP_3R -mediated increases in $[\text{Ca}^{2+}]_i$.

(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 ($[\text{Ca}^{2+}]_{\text{S/ER}}$), the $[\text{Ca}^{2+}]_{\text{S/ER}}$ sensor STIM1 undergoes dynamic spatial reorganization into aggregate clusters that interact with Orai1 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 (Orai1 α) and a 23 kDa short form (Orai1 β) (Fukushima, Tomita, Janoshazi, & Putney, 2012). Perhaps as a result of these proteomic and functional differences, Orai1 α 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 Å 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-Spezia, 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 upregulation 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 PDGF β receptor and downstream PLC γ -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 $\text{Ca}_v1.2$ 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 Å 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 $\beta 1$ subunit reduces BK_{Ca} Ca^{2+} sensitivity resulting in impaired STOC activity, increased myogenic tone, and hypertension (Amberg, Bonev, Rossow, Nelson, & Santana, 2003; Nieves-Cintrón, Amberg, Nichols, Molkentin, & Santana, 2007). The coupling strength between RyR and BK_{Ca} 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 ($\text{IP}_3\text{R1}$, $\text{IP}_3\text{R2}$, $\text{IP}_3\text{R3}$) have been reported (Narayanan et al., 2012). While expression of all three isoforms has been found in VSM from aorta, mesenteric, and cerebral arteries, $\text{IP}_3\text{R1}$ seems to be the predominant isoform in VSM from small resistance

arteries (Grayson, Haddock, Murray, Wojcikiewicz, & Hill, 2004; Zhao, Adebisi, Blaskova, Xi, & Jaggar, 2008; Zhou et al., 2008). Yet, the expression profile of the IP₃R isoforms can vary depending on the developmental stage. Accordingly, expression of IP₃R3 is high in neonatal SM, decreases during development, and is surpassed by increasing IP₃R1 expression in adult SM (Tasker, Michelangeli, & Nixon, 1999). High levels of IP₃R2 and IP₃R3 expression have also been found in proliferating SM (Tasker, Taylor, & Nixon, 2000). These IP₃R isoforms also differ in IP₃-binding affinities as follows: IP₃R2 > IP₃R1 > IP₃R3 (Newton, Mignery, & Sudhof, 1994; Wojcikiewicz & Luo, 1998). Physical localization of IP₃R 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).

IP₃R activation is stimulated by the second messenger IP₃, which results from the hydrolysis of phosphatidylinositol 4,5-bisphosphate by PLC in response to activation of G_{q/11}-coupled receptors. Indeed, IP₃R activity in VSM can be stimulated by many endogenous vasoactive molecules that act through G_{q/11}-coupled receptors to produce IP₃, including ET-1, acetylcholine, noradrenaline, and serotonin (Berridge, 2008). Pharmacological inhibition of IP₃R can be achieved with the application of widely used agents such as 2-APB and xestospongins. IP₃R inhibition may have distinct effects on vascular reactivity. For instance, in mouse mesenteric arteries, IP₃R inhibition with xestospongins did not affect the myogenic tone, but did prevent the phenylephrine-induced vasoconstriction (Mauban, Zacharia, Fairfax, & Wier, 2015). IP₃R activity in VSM can be modulated by [Ca²⁺]_i, luminal SR Ca²⁺ 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 IP₃R can produce multiple Ca²⁺ signals, including Ca²⁺ puffs and Ca²⁺ waves, with important implications for VSM function. Ca²⁺ puffs are elementary, localized Ca²⁺ release events produced by clusters of IP₃R (Parker & Smith, 2010; Tovey et al., 2001). Ca²⁺ 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 IP₃R localization, distribution, and function. Yet, recent indirect evidence suggests that Ca²⁺ puffs could alter cerebral VSM function through modulation of plasmalemmal ion channel activity. Accordingly, localized Ca²⁺ release via IP₃R 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 $[\text{Ca}^{2+}]_i$ 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 $[\text{Ca}^{2+}]_i$ 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 PLC γ 1 in this process, albeit via distinct signaling pathways. One study implicates pressure-induced stimulation of PLC γ 1 activity to TRPC6-mediated Ca^{2+} influx leading to activation (via CICR) of IP_3 -sensitized IP_3R . The resulting localized rise in $[\text{Ca}^{2+}]_i$ 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 PLC γ 1, 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 MLC₂₀ 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 $\text{IP}_3\text{R}1$ 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.

IP_3R -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 $\text{IP}_3\text{R}1$ (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 IP_3R , but no changes in IP_3R expression, contributed to agonist-induced

vasoconstriction during hypertension, and that this did not require IP₃R-mediated SR Ca²⁺ 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 IP₃R expression, function, and IP₃R-mediated Ca²⁺ signals in VSM have also been documented to contribute to vascular dysfunction during diabetes and atherosclerosis (Massaelli, Austria, & Pierce, 1999; Searls, Loganathan, Smirnova, & Stehno-Bittel, 2010). Thus, IP₃R-mediated SR Ca²⁺ release-dependent and -independent mechanisms may also contribute to impaired VSM function during pathological conditions.

4. MITOCHONDRIAL Ca²⁺ CHANNELS

Intracellular organelles like mitochondria are emerging as important players in smooth muscle Ca²⁺ handling. Mitochondria harbor various Ca²⁺ channels executing mitochondrial Ca²⁺ turnover. Mitochondrial-calcium-uniporter (MCU), mitochondrial RyR, mitochondrial-Ca²⁺-channel type-2, rapid mode of uptake, and H⁺/Ca²⁺ exchanger (Letm1) play a major role in mitochondrial Ca²⁺ influx. The notable channels for mitochondrial Ca²⁺ extrusion include mitochondrial Na⁺/Ca²⁺ exchanger, mitochondrial permeability transition pores (mPTPs), and Letm1 (which works as an efflux channel at high mitochondrial Ca²⁺ concentrations ([Ca²⁺]_{mito})) (Hoppe, 2010). These mitochondrial Ca²⁺ 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 Ca²⁺ over a wide concentration range (200 nM–10 μM) through the highly Ca²⁺-selective channel MCU. Mitochondrial Ca²⁺ 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 Ca²⁺ elevation, thereby contributing to intracellular Ca²⁺ homeostasis (Gilbert, Ducret, Marthan, Savineau, & Quignard, 2014). Additionally, evidence suggests that mitochondria do not readily buffer the initial stage of Ca²⁺ influx through LTCC, but rather affect the declining phase of the LTCC-mediated Ca²⁺ signal. However, the organelle is far quicker to scavenge the Ca²⁺ release into the cytosol

through IP₃R, thereby targeting the rising phase of Ca²⁺ transient produced by these receptors. Such buffering action may prevent Ca²⁺-dependent deactivation of IP₃R in VSM, thereby allowing repeated occurrence of IP₃R-mediated Ca²⁺ oscillation and Ca²⁺ waves (McCarron et al., 2013). The cue to distinguish the mitochondrial buffering effect on LTCC Ca²⁺ signals vs IP₃R Ca²⁺ signals may lie in a seminal work in neurons that highlights the differential Ca²⁺ sequestering effect of mitochondria on Ca_v1 and Ca_v2 channels solely based on the positional/spatial aspect of the organelle with respect to the ion channel (Wheeler et al., 2012). Interestingly, Ca²⁺ 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, Ca²⁺ intake by mitochondria residing at close proximity of the IP₃R causes depolarization of the organelle through an elevation in [Ca²⁺]_{mito}, thereby culminating in increased production of ROS and NF-κB activation (Narayanan, Xi, Pfeffer, & Jaggar, 2010). NF-κB 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 Ca²⁺ influx and vasoconstriction (Chaplin, Nieves-Cintrón, 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 Ca²⁺ channels, as well as their interplay with other ion channels in modulating cellular Ca²⁺ signals and VSM function.

5. CONCLUSION

Intracellular Ca²⁺ VSM is controlled by an exquisite repertoire of Ca²⁺-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.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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REFERENCES

- Abd El-Rahman, R. R., Harraz, O. F., Brett, S. E., Anfinogenova, Y., Mufti, R. E., Goldman, D., & Welsh, D. G. (2013). Identification of L- and T-type Ca^{2+} channels in rat cerebral arteries: Role in myogenic tone development. *American Journal of*

- Physiology. Heart and Circulatory Physiology*, 304(1), H58–H71. <http://dx.doi.org/10.1152/ajpheart.00476.2012>.
- Abdi, A., Mazzocco, C., Legeron, F. P., Yvert, B., Macrez, N., & Morel, J. L. (2015). TRPP2 modulates ryanodine- and inositol-1,4,5-trisphosphate receptors-dependent Ca^{2+} signals in opposite ways in cerebral arteries. *Cell Calcium*, 58, 467–475.
- Abou-Saleh, H., Pathan, A. R., Daalis, A., Hubrack, S., Abou-Jassoum, H., Al-Naeimi, H., ... Machaca, K. (2013). Inositol 1,4,5-trisphosphate (IP3) receptor up-regulation in hypertension is associated with sensitization of Ca^{2+} release and vascular smooth muscle contractility. *Journal of Biological Chemistry*, 288(46), 32941–32951. <http://dx.doi.org/10.1074/jbc.M113.496802>.
- Adebiyi, A., Thomas-Gatewood, C. M., Leo, M. D., Kidd, M. W., Neeb, Z. P., & Jaggar, J. H. (2012). An elevation in physical coupling of type 1 inositol 1,4,5-trisphosphate (IP3) receptors to transient receptor potential 3 (TRPC3) channels constricts mesenteric arteries in genetic hypertension. *Hypertension*, 60(5), 1213–1219. <http://dx.doi.org/10.1161/HYPERTENSIONAHA.112.198820>.
- Adebiyi, A., Zhao, G., Narayanan, D., Thomas-Gatewood, C. M., Bannister, J. P., & Jaggar, J. H. (2010). Isoform-selective physical coupling of TRPC3 channels to IP3 receptors in smooth muscle cells regulates arterial contractility. *Circulation Research*, 106(10), 1603–1612. <http://dx.doi.org/10.1161/CIRCRESAHA.110.216804>.
- Akaike, N., Kanaide, H., Kuga, T., Nakamura, M., Sadoshima, J., & Tomoike, H. (1989). Low-voltage-activated calcium current in rat aorta smooth muscle cells in primary culture. *Journal of Physiology*, 416, 141–160.
- Amberg, G. C., Bonev, A. D., Rossow, C. F., Nelson, M. T., & Santana, L. F. (2003). Modulation of the molecular composition of large conductance, Ca^{2+} activated K^{+} channels in vascular smooth muscle during hypertension. *Journal of Clinical Investigation*, 112(5), 717–724.
- Amberg, G. C., Earley, S., & Glapa, S. A. (2010). Local regulation of arterial L-type calcium channels by reactive oxygen species. *Circulation Research*, 107(8), 1002–1010. <http://dx.doi.org/10.1161/CIRCRESAHA.110.217018>.
- Amberg, G. C., & Navedo, M. F. (2013). Calcium dynamics in vascular smooth muscle. *Microcirculation*, 20(4), 281–289. <http://dx.doi.org/10.1111/micc.12046>.
- Amberg, G. C., Navedo, M. F., Nieves-Cintrón, M., Molkentin, J. D., & Santana, L. F. (2007). Calcium sparklets regulate local and global calcium in murine arterial smooth muscle. *Journal of Physiology*, 579(1), 187–201.
- Arikkath, J., & Campbell, K. P. (2003). Auxiliary subunits: Essential components of the voltage-gated calcium channel complex. *Current Opinion in Neurobiology*, 13(3), 298–307.
- Bannister, J. P., Adebiyi, A., Zhao, G., Narayanan, D., Thomas, C. M., Feng, J. Y., & Jaggar, J. H. (2009). Smooth muscle cell $\alpha 2\delta 1$ subunits are essential for vasoregulation by $\text{CaV}1.2$ channels. *Circulation Research*, 105, 948–955.
- Bannister, J. P., Bulley, S., Narayanan, D., Thomas-Gatewood, C., Luzny, P., Pachau, J., & Jaggar, J. H. (2012). Transcriptional upregulation of $\alpha 2\delta 1$ elevates arterial smooth muscle cell voltage-dependent Ca^{2+} channel surface expression and cerebrovascular constriction in genetic hypertension. *Hypertension*, 60(4), 1006–1015. <http://dx.doi.org/10.1161/HYPERTENSIONAHA.112.199661>.
- Bannister, J. P., Leo, M. D., Narayanan, D., Jangsangthong, W., Nair, A., Evanson, K. W., ... Jaggar, J. H. (2013). The voltage-dependent L-type Ca^{2+} ($\text{CaV}1.2$) channel C-terminus fragment is a bi-modal vasodilator. *Journal of Physiology*, 591(Pt. 12), 2987–2998. <http://dx.doi.org/10.1113/jphysiol.2013.251926>.
- Baylie, R. L., & Brayden, J. E. (2011). TRPV channels and vascular function. *Acta Physiologica (Oxford, England)*, 203(1), 99–116. <http://dx.doi.org/10.1111/j.1748-1716.2010.02217.x>.

- Bayliss, W. M. (1902). On the local reaction of the arterial wall to changes in internal pressure. *Journal of Physiology*, 28, 220–231.
- Bergdahl, A., Gomez, M. F., Dreja, K., Xu, S. Z., Adner, M., Beech, D. J., ... Sward, K. (2003). Cholesterol depletion impairs vascular reactivity to endothelin-1 by reducing store-operated Ca^{2+} entry dependent on TRPC1. *Circulation Research*, 93(9), 839–847. <http://dx.doi.org/10.1161/01.RES.0000100367.45446.A3>.
- Bergdahl, A., Gomez, M. F., Wihlborg, A. K., Erlinge, D., Eyjolfson, A., Xu, S. Z., ... Hellstrand, P. (2005). Plasticity of TRPC expression in arterial smooth muscle: Correlation with store-operated Ca^{2+} entry. *American Journal of Physiology. Cell Physiology*, 288(4), C872–C880. <http://dx.doi.org/10.1152/ajpcell.00334.2004>.
- Berra-Romani, R., Mazzocco-Spezia, A., Pulina, M. V., & Golovina, V. A. (2008). Ca^{2+} handling is altered when arterial myocytes progress from a contractile to a proliferative phenotype in culture. *American Journal of Physiology. Cell Physiology*, 295(3), C779–C790. <http://dx.doi.org/10.1152/ajpcell.00173.2008>.
- Berridge, M. J. (2008). Smooth muscle cell calcium activation mechanisms. *Journal of Physiology*, 586(21), 5047–5061. <http://dx.doi.org/10.1113/jphysiol.2008.160440>.
- Bezannilla, F. (2008). How membrane proteins sense voltage. *Nature Reviews. Molecular Cell Biology*, 9(4), 323–332. <http://dx.doi.org/10.1038/nrm2376>.
- Bezprozvanny, I., Watras, J., & Ehrlich, B. E. (1991). Bell-shaped calcium-response curves of $\text{Ins}(1,4,5)\text{P}_3$ - and calcium-gated channels from endoplasmic reticulum of cerebellum. *Nature*, 351(6329), 751–754. <http://dx.doi.org/10.1038/351751a0>.
- Biel, M., Ruth, P., Bosse, E., Hullin, R., Stuhmer, W., Flockerzi, V., & Hofmann, F. (1990). Primary structure and functional expression of a high voltage activated calcium channel from rabbit lung. *FEBS Letters*, 269(2), 409–412.
- Boittin, F. X., Coussin, F., Morel, J. L., Halet, G., Macrez, N., & Mironneau, J. (2000). $\text{Ca}(2+)$ signals mediated by $\text{Ins}(1,4,5)\text{P}_3$ -gated channels in rat ureteric myocytes. *Biochemical Journal*, 349(Pt 1), 323–332.
- Boittin, F. X., Macrez, N., Halet, G., & Mironneau, J. (1999). Norepinephrine-induced $\text{Ca}(2+)$ waves depend on InsP_3 and ryanodine receptor activation in vascular myocytes. *American Journal of Physiology*, 277(1 Pt 1), C139–C151.
- Bonev, A. D., Jaggar, J. H., Rubart, M., & Nelson, M. T. (1997). Activators of protein kinase C decrease Ca^{2+} spark frequency in smooth muscle cells from cerebral arteries. *American Journal of Physiology*, 273(6 Pt 1), C2090–C2095.
- Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D., & Julius, D. (1997). The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature*, 389(6653), 816–824. <http://dx.doi.org/10.1038/39807>.
- Catterall, W. A. (2011). Voltage-gated calcium channels. *Cold Spring Harbor Perspectives in Biology*, 3(8), a003947. <http://dx.doi.org/10.1101/cshperspect.a003947>.
- Cavanaugh, D. J., Chesler, A. T., Jackson, A. C., Sigal, Y. M., Yamanaka, H., Grant, R., ... Basbaum, A. I. (2011). Trpv1 reporter mice reveal highly restricted brain distribution and functional expression in arteriolar smooth muscle cells. *Journal of Neuroscience*, 31(13), 5067–5077. <http://dx.doi.org/10.1523/JNEUROSCI.6451-10.2011>.
- Chalmers, S., & McCarron, J. G. (2008). The mitochondrial membrane potential and Ca^{2+} oscillations in smooth muscle. *Journal of Cell Science*, 121(Pt 1), 75–85. <http://dx.doi.org/10.1242/jcs.014522>.
- Chaplin, N. L., Nieves-Cintrón, M., Fresquez, A. M., Navedo, M. F., & Amberg, G. C. (2015). Arterial smooth muscle mitochondria amplify hydrogen peroxide microdomains functionally coupled to L-type calcium channels. *Circulation Research*, 117(12), 1013–1023. <http://dx.doi.org/10.1161/CIRCRESAHA.115.306996>.
- Cheng, X., Liu, J., Asuncion-Chin, M., Blaskova, E., Bannister, J. P., Dopico, A. M., & Jaggar, J. H. (2007). A novel $\text{Ca}(V)1.2$ N terminus expressed in smooth muscle cells of resistance size arteries modifies channel regulation by auxiliary subunits.

- Journal of Biological Chemistry*, 282(40), 29211–29221. <http://dx.doi.org/10.1074/jbc.M610623200>.
- Cheranov, S. Y., & Jaggar, J. H. (2004). Mitochondrial modulation of Ca^{2+} sparks and transient KCa currents in smooth muscle cells of rat cerebral arteries. *Journal of Physiology*, 556(Pt 3), 755–771. <http://dx.doi.org/10.1113/jphysiol.2003.059568>.
- Collier, M. L., Ji, G., Wang, Y., & Kotlikoff, M. I. (2000). Calcium-induced calcium release in smooth muscle: Loose coupling between the action potential and calcium release. *Journal of General Physiology*, 115(5), 653–662.
- Coussin, F., Macrez, N., Morel, J. L., & Mironneau, J. (2000). Requirement of ryanodine receptor subtypes 1 and 2 for Ca^{2+} -induced Ca^{2+} release in vascular myocytes. *Journal of Biological Chemistry*, 275(13), 9596–9603.
- Dabertrand, F., Nelson, M. T., & Brayden, J. E. (2012). Acidosis dilates brain parenchymal arterioles by conversion of calcium waves to sparks to activate BK channels. *Circulation Research*, 110(2), 285–294. <http://dx.doi.org/10.1161/CIRCRESAHA.111.258145>.
- DeHaven, W. I., Jones, B. F., Petranks, J. G., Smyth, J. T., Tomita, T., Bird, G. S., & Putney, J. W., Jr. (2009). TRPC channels function independently of STIM1 and Orai1. *Journal of Physiology*, 587(Pt. 10), 2275–2298. <http://dx.doi.org/10.1113/jphysiol.2009.170431>.
- Derler, I., Schindl, R., Fritsch, R., Heftberger, P., Riedl, M. C., Begg, M., ... Romanin, C. (2013). The action of selective CRAC channel blockers is affected by the Orai pore geometry. *Cell Calcium*, 53(2), 139–151. <http://dx.doi.org/10.1016/j.ceca.2012.11.005>.
- Desai, P. N., Zhang, X., Wu, S., Janoshazi, A., Bolimuntha, S., Putney, J. W., & Trebak, M. (2015). Multiple types of calcium channels arising from alternative translation initiation of the Orai1 message. *Science Signaling*, 8(387), ra74. <http://dx.doi.org/10.1126/scisignal.aaa8323>.
- Dietrich, A., Kalwa, H., Storch, U., Mederos y Schnitzler, M., Salanova, B., Pinkenburg, O., ... Gudermann, T. (2007). Pressure-induced and store-operated cation influx in vascular smooth muscle cells is independent of TRPC1. *Pflügers Archiv*, 455(3), 465–477. <http://dx.doi.org/10.1007/s00424-007-0314-3>.
- Dong, X. P., Wang, X., & Xu, H. (2010). TRP channels of intracellular membranes. *Journal of Neurochemistry*, 113(2), 313–328. <http://dx.doi.org/10.1111/j.1471-4159.2010.06626.x>.
- Earley, S., & Brayden, J. E. (2015). Transient receptor potential channels in the vasculature. *Physiological Reviews*, 95(2), 645–690. <http://dx.doi.org/10.1152/physrev.00026.2014>.
- Earley, S., Heppner, T. J., Nelson, M. T., & Brayden, J. E. (2005). TRPV4 forms a novel Ca^{2+} signaling complex with ryanodine receptors and BKCa channels. *Circulation Research*, 97(12), 1270–1279.
- Earley, S., Pauyo, T., Drapp, R., Tavares, M. J., Liedtke, W., & Brayden, J. E. (2009). TRPV4-dependent dilation of peripheral resistance arteries influences arterial pressure. *American Journal of Physiology. Heart and Circulatory Physiology*, 297(3), H1096–H1102. <http://dx.doi.org/10.1152/ajpheart.00241.2009>.
- Earley, S., Straub, S. V., & Brayden, J. (2007). Protein kinase C regulates vascular myogenic tone through activation of TRPM4. *American Journal of Physiology, Heart and Circulatory Physiology*, 292(6), H2613–H2622.
- Earley, S., Waldron, B. J., & Brayden, J. E. (2004). Critical role for transient receptor potential channel TRPM4 in myogenic constriction of cerebral arteries. *Circulation Research*, 95(9), 922–929.
- Efendiev, R., Bavencoffe, A., Hu, H., Zhu, M. X., & Dessauer, C. W. (2013). Scaffolding by A-kinase anchoring protein enhances functional coupling between adenylyl cyclase and TRPV1 channel. *Journal of Biological Chemistry*, 288(6), 3929–3937. <http://dx.doi.org/10.1074/jbc.M112.428144>.
- Efremov, R. G., Leitner, A., Aebersold, R., & Raunser, S. (2015). Architecture and conformational switch mechanism of the ryanodine receptor. *Nature*, 517(7532), 39–43. <http://dx.doi.org/10.1038/nature13916>.

- Essin, K., Welling, A., Hofmann, F., Luft, F. C., Gollasch, M., & Moosmang, S. (2007). Indirect coupling between Cav1.2 channels and RyR to generate Ca^{2+} sparks in murine arterial smooth muscle cells. *Journal of Physiology*, 584(Pt 1), 205–219.
- Fan, G., Baker, M. L., Wang, Z., Baker, M. R., Sinyagovskiy, P. A., Chiu, W., ... Serysheva, I. I. (2015). Gating machinery of InsP3R channels revealed by electron cryomicroscopy. *Nature*, 527(7578), 336–341. <http://dx.doi.org/10.1038/nature15249>.
- Fernandez, J. A., McGahon, M. K., McGeown, J. G., & Curtis, T. M. (2015). CaV3.1 T-type Ca^{2+} channels contribute to myogenic signaling in rat retinal arterioles. *Investigative Ophthalmology & Visual Science*, 56(9), 5125–5132. <http://dx.doi.org/10.1167/iovs.15-17299>.
- Frischauf, I., Muik, M., Derler, I., Bergsmann, J., Fahrner, M., Schindl, R., ... Romanin, C. (2009). Molecular determinants of the coupling between STIM1 and Orai channels: Differential activation of Orai1–3 channels by a STIM1 coiled-coil mutant. *Journal of Biological Chemistry*, 284(32), 21696–21706. <http://dx.doi.org/10.1074/jbc.M109.018408>.
- Fukushima, M., Tomita, T., Janoshazi, A., & Putney, J. W. (2012). Alternative translation initiation gives rise to two isoforms of Orai1 with distinct plasma membrane mobilities. *Journal of Cell Science*, 125(Pt. 18), 4354–4361. <http://dx.doi.org/10.1242/jcs.104919>.
- Gaudet, R. (2008). A primer on ankyrin repeat function in TRP channels and beyond. *Molecular Biosystems*, 4(5), 372–379. <http://dx.doi.org/10.1039/b801481g>.
- Gilbert, G., Ducret, T., Marthan, R., Savineau, J. P., & Quignard, J. F. (2014). Stretch-induced Ca^{2+} signalling in vascular smooth muscle cells depends on Ca^{2+} store segregation. *Cardiovascular Research*, 103(2), 313–323. <http://dx.doi.org/10.1093/cvr/cvu069>.
- Gonzales, A. L., Amberg, G. C., & Earley, S. (2010). Ca^{2+} release from the sarcoplasmic reticulum is required for sustained TRPM4 activity in cerebral artery smooth muscle cells. *American Journal of Physiology. Cell Physiology*, 299(2), C279–C288. <http://dx.doi.org/10.1152/ajpcell.00550.2009>.
- Gonzales, A. L., & Earley, S. (2012). Endogenous cytosolic Ca^{2+} buffering is necessary for TRPM4 activity in cerebral artery smooth muscle cells. *Cell Calcium*, 51(1), 82–93. <http://dx.doi.org/10.1016/j.ceca.2011.11.004>.
- Gonzales, A. L., Yang, Y., Sullivan, M. N., Sanders, L., Dabertrand, F., Hill-Eubanks, D. C., ... Earley, S. (2014). A PLCgamma1-dependent, force-sensitive signaling network in the myogenic constriction of cerebral arteries. *Science Signaling*, 7(327), ra49. <http://dx.doi.org/10.1126/scisignal.2004732>.
- Gordienko, D. V., & Bolton, T. B. (2002). Crosstalk between ryanodine receptors and IP(3) receptors as a factor shaping spontaneous Ca^{2+} -release events in rabbit portal vein myocytes. *Journal of Physiology*, 542(Pt. 3), 743–762.
- Gray, L. S., & Macdonald, T. L. (2006). The pharmacology and regulation of T type calcium channels: New opportunities for unique therapeutics for cancer. *Cell Calcium*, 40(2), 115–120. <http://dx.doi.org/10.1016/j.ceca.2006.04.014>.
- Grayson, T. H., Haddock, R. E., Murray, T. P., Wojcikiewicz, R. J., & Hill, C. E. (2004). Inositol 1,4,5-trisphosphate receptor subtypes are differentially distributed between smooth muscle and endothelial layers of rat arteries. *Cell Calcium*, 36(6), 447–458. <http://dx.doi.org/10.1016/j.ceca.2004.04.005>.
- Gurnett, C. A., De Waard, M., & Campbell, K. P. (1996). Dual function of the voltage-dependent Ca^{2+} channel $\alpha 2$ delta subunit in current stimulation and subunit interaction. *Neuron*, 16(2), 431–440.
- Gustafsson, F., Andreassen, D., Salomonsson, M., Jensen, B. L., & Holstein-Rathlou, N. (2001). Conducted vasoconstriction in rat mesenteric arterioles: Role for dihydropyridine-insensitive Ca^{2+} channels. *American Journal of Physiology. Heart and Circulatory Physiology*, 280(2), H582–H590.
- Harraz, O. F., Abd El-Rahman, R. R., Bigdely-Shamloo, K., Wilson, S. M., Brett, S. E., Romero, M., ... Welsh, D. G. (2014). $\text{Ca(V)}3.2$ channels and the induction of negative

- feedback in cerebral arteries. *Circulation Research*, 115(7), 650–661. <http://dx.doi.org/10.1161/CIRCRESAHA.114.304056>.
- Harraz, O. F., Brett, S. E., & Welsh, D. G. (2014). Nitric oxide suppresses vascular voltage-gated T-type Ca^{2+} channels through cGMP/PKG signaling. *American Journal of Physiology. Heart and Circulatory Physiology*, 306(2), H279–H285. <http://dx.doi.org/10.1152/ajpheart.00743.2013>.
- Harraz, O. F., Brett, S. E., Zechariah, A., Romero, M., Puglisi, J. L., Wilson, S. M., & Welsh, D. G. (2015). Genetic ablation of $\text{CaV}3.2$ channels enhances the arterial myogenic response by modulating the RyR-BKCa axis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 35(8), 1843–1851. <http://dx.doi.org/10.1161/ATVBAHA.115.305736>.
- Harraz, O. F., Visser, F., Brett, S. E., Goldman, D., Zechariah, A., Hashad, A. M., ... Welsh, D. G. (2015). $\text{CaV}1.2/\text{CaV}3.x$ channels mediate divergent vasomotor responses in human cerebral arteries. *Journal of General Physiology*, 145(5), 405–418. <http://dx.doi.org/10.1085/jgp.201511361>.
- Harraz, O. F., & Welsh, D. G. (2013a). Protein kinase A regulation of T-type Ca^{2+} channels in rat cerebral arterial smooth muscle. *Journal of Cell Science*, 126(Pt. 13), 2944–2954. <http://dx.doi.org/10.1242/jcs.128363>.
- Harraz, O. F., & Welsh, D. G. (2013b). T-type Ca^{2+} channels in cerebral arteries: Approaches, hypotheses, and speculation. *Microcirculation*, 20(4), 299–306. <http://dx.doi.org/10.1111/micc.12038>.
- He, Y., Yao, G., Savoia, C., & Touyz, R. M. (2005). Transient receptor potential melastatin 7 ion channels regulate magnesium homeostasis in vascular smooth muscle cells: Role of angiotensin II. *Circulation Research*, 96(2), 207–215. <http://dx.doi.org/10.1161/01.RES.0000152967.88472.3e>.
- Helliwell, R. M., & Large, W. A. (1997). Alpha 1-adrenoceptor activation of a non-selective cation current in rabbit portal vein by 1,2-diacyl-sn-glycerol. *Journal of Physiology*, 499(Pt. 2), 417–428.
- Hill-Eubanks, D. C., Werner, M. E., Heppner, T. J., & Nelson, M. T. (2011). Calcium signaling in smooth muscle. *Cold Spring Harbor Perspectives in Biology*, 3(9), a004549. <http://dx.doi.org/10.1101/cshperspect.a004549>.
- Hooper, R., Zhang, X., Webster, M., Go, C., Kedra, J., Marchbank, K., ... Soboloff, J. (2015). Novel protein kinase C-mediated control of Orail function in invasive melanoma. *Molecular and Cellular Biology*, 35(16), 2790–2798. <http://dx.doi.org/10.1128/MCB.01500-14>.
- Hoppe, U. C. (2010). Mitochondrial calcium channels. *FEBS Letters*, 584(10), 1975–1981. <http://dx.doi.org/10.1016/j.febslet.2010.04.017>.
- Hoth, M., & Penner, R. (1993). Calcium release-activated calcium current in rat mast cells. *Journal of Physiology*, 465, 359–386.
- Hou, X., Pedi, L., Diver, M. M., & Long, S. B. (2012). Crystal structure of the calcium release-activated calcium channel Orail. *Science*, 338(6112), 1308–1313. <http://dx.doi.org/10.1126/science.1228757>.
- Hwa, J. J., & Bevan, J. A. (1986). Dihydropyridine calcium agonists selectively enhance resistance artery myogenic tone. *European Journal of Pharmacology*, 126(3), 231–238.
- Iino, M. (1990). Biphasic Ca^{2+} dependence of inositol 1,4,5-trisphosphate-induced Ca release in smooth muscle cells of the guinea pig taenia caeci. *Journal of General Physiology*, 95(6), 1103–1122.
- Inoue, R., Jensen, L. J., Shi, J., Morita, H., Nishida, M., Honda, A., & Ito, Y. (2006). Transient receptor potential channels in cardiovascular function and disease. *Circulation Research*, 99(2), 119–131. <http://dx.doi.org/10.1161/01.RES.0000233356.10630.8a>.
- Inoue, R., Okada, T., Onoue, H., Hara, Y., Shimizu, S., Naitoh, S., ... Mori, Y. (2001). The transient receptor potential protein homologue TRP6 is the essential component of

- vascular $\alpha(1)$ -adrenoceptor-activated $\text{Ca}(2+)$ -permeable cation channel. *Circulation Research*, 88(3), 325–332.
- Jaggard, J. H. (2001). Intravascular pressure regulates local and global $\text{Ca}(2+)$ signaling in cerebral artery smooth muscle cells. *American Journal of Physiology Cell Physiology*, 281(2), C439–C448.
- Jaggard, J. H., & Nelson, M. T. (2000). Differential regulation of Ca^{2+} sparks and Ca^{2+} waves by UTP in rat cerebral artery smooth muscle cells. *American Journal of Physiology. Cell Physiology*, 279(5), C1528–C1539.
- Jaggard, J. H., Porter, V. A., Lederer, W. J., & Nelson, M. T. (2000). Calcium sparks in smooth muscle. *American Journal of Physiology. Cell Physiology*, 278(2), C235–C256.
- Jensen, L. J., Salomonsson, M., Jensen, B. L., & Holstein-Rathlou, N. H. (2004). Depolarization-induced calcium influx in rat mesenteric small arterioles is mediated exclusively via mibefradil-sensitive calcium channels. *British Journal of Pharmacology*, 142(4), 709–718. <http://dx.doi.org/10.1038/sj.bjp.0705841>.
- Keef, K. D., Hume, J. R., & Zhong, J. (2001). Regulation of cardiac and smooth muscle $\text{Ca}(2+)$ channels ($\text{Ca}(V)1.2a, b$) by protein kinases. *American Journal of Physiology. Cell Physiology*, 281(6), C1743–C1756.
- Kharade, S. V., Sonkusare, S. K., Srivastava, A. K., Thakali, K. M., Fletcher, T. W., Rhee, S. W., & Rusch, N. J. (2013). The $\beta 3$ subunit contributes to vascular calcium channel upregulation and hypertension in angiotensin II-infused C57BL/6 mice. *Hypertension*, 61(1), 137–142. <http://dx.doi.org/10.1161/HYPERTENSIONAHA.112.197863>.
- Kimura, M., Obara, K., Sasase, T., Ishikawa, T., Tanabe, Y., & Nakayama, K. (2000). Specific inhibition of stretch-induced increase in L-type calcium channel currents by herbimycin A in canine basilar arterial myocytes. *British Journal of Pharmacology*, 130(4), 923–931. <http://dx.doi.org/10.1038/sj.bjp.0703360>.
- Klugebauer, N., Lacinova, L., Marais, E., Hobom, M., & Hofmann, F. (1999). Molecular diversity of the calcium channel $\alpha 2\delta$ subunit. *Journal of Neuroscience*, 19(2), 684–691.
- Knot, H. J., & Nelson, M. T. (1998). Regulation of arterial diameter and wall $[\text{Ca}^{2+}]$ in cerebral arteries of rat by membrane potential and intravascular pressure. *Journal of Physiology*, 508(Pt. 1), 199–209.
- Koda, K., Hyakkoku, K., Ogawa, K., Takasu, K., Imai, S., Sakurai, Y., ... Morioka, Y. (2016). Sensitization of TRPV1 by protein kinase C in rats with mono-iodoacetate-induced joint pain. *Osteoarthritis and Cartilage*, 24(7), 1254–1262. <http://dx.doi.org/10.1016/j.joca.2016.02.010>.
- Koulen, P., Cai, Y., Geng, L., Maeda, Y., Nishimura, S., Witzgall, R., ... Somlo, S. (2002). Polycystin-2 is an intracellular calcium release channel. *Nature Cell Biology*, 4(3), 191–197. <http://dx.doi.org/10.1038/ncb754>.
- Kuo, I. Y., Ellis, A., Seymour, V. A., Sandow, S. L., & Hill, C. E. (2010). Dihydropyridine-insensitive calcium currents contribute to function of small cerebral arteries. *Journal of Cerebral Blood Flow and Metabolism*, 30(6), 1226–1239. <http://dx.doi.org/10.1038/jcbfm.2010.11>.
- Kwan, H. Y., Shen, B., Ma, X., Kwok, Y. C., Huang, Y., Man, Y. B., ... Yao, X. (2009). TRPC1 associates with BK(Ca) channel to form a signal complex in vascular smooth muscle cells. *Circulation Research*, 104(5), 670–678. <http://dx.doi.org/10.1161/CIRCRESAHA.108.188748>.
- Lamont, C., & Wier, W. G. (2004). Different roles of ryanodine receptors and inositol (1,4,5)-trisphosphate receptors in adrenergically stimulated contractions of small arteries. *American Journal of Physiology. Heart and Circulatory Physiology*, 287(2), H617–H625. <http://dx.doi.org/10.1152/ajpheart.00708.2003>.
- Lange, I., Yamamoto, S., Partida-Sanchez, S., Mori, Y., Fleig, A., & Penner, R. (2009). TRPM2 functions as a lysosomal Ca^{2+} -release channel in beta cells. *Science Signaling*, 2(71), ra23. <http://dx.doi.org/10.1126/scisignal.2000278>.

- Lanner, J. T., Georgiou, D. K., Joshi, A. D., & Hamilton, S. L. (2010). Ryanodine receptors: Structure, expression, molecular details, and function in calcium release. *Cold Spring Harbor Perspectives in Biology*, 2(11), a003996. <http://dx.doi.org/10.1101/cshperspect.a003996>.
- Lee, J. H., Gomora, J. C., Cribbs, L. L., & Perez-Reyes, E. (1999). Nickel block of three cloned T-type calcium channels: Low concentrations selectively block α_1H . *Biophysical Journal*, 77(6), 3034–3042.
- Li, Y., & Brayden, J. E. (2015). Rho kinase activity governs arteriolar myogenic depolarization. *Journal of Cerebral Blood Flow and Metabolism*. <http://dx.doi.org/10.1177/0271678X15621069>, Epub ahead of print.
- Li, J., McKeown, L., Ojelabi, O., Stacey, M., Foster, R., O'Regan, D., ... Beech, D. J. (2011). Nanomolar potency and selectivity of a $Ca(2)(+)$ release-activated $Ca(2)(+)$ channel inhibitor against store-operated $Ca(2)(+)$ entry and migration of vascular smooth muscle cells. *British Journal of Pharmacology*, 164(2), 382–393. <http://dx.doi.org/10.1111/j.1476-5381.2011.01368.x>.
- Liao, M., Cao, E., Julius, D., & Cheng, Y. (2013). Structure of the TRPV1 ion channel determined by electron cryo-microscopy. *Nature*, 504(7478), 107–112. <http://dx.doi.org/10.1038/nature12822>.
- Liao, P., Yu, D., Li, G., Yong, T. F., Soon, J. L., Chua, Y. L., & Soong, T. W. (2007). A smooth muscle Cav1.2 calcium channel splice variant underlies hyperpolarized window current and enhanced state-dependent inhibition by nifedipine. *Journal of Biological Chemistry*, 282(48), 35133–35142. <http://dx.doi.org/10.1074/jbc.M705478200>.
- Lindsey, S. H., & Songu-Mize, E. (2010). Stretch-induced TRPC4 downregulation is accompanied by reduced capacitative Ca^{2+} entry in WKY but not SHR mesenteric smooth muscle cells. *Clinical and Experimental Hypertension*, 32(5), 288–292. <http://dx.doi.org/10.3109/10641960903443525>.
- Massaelli, H., Austria, J. A., & Pierce, G. N. (1999). Chronic exposure of smooth muscle cells to minimally oxidized LDL results in depressed inositol 1,4,5-trisphosphate receptor density and $Ca(2+)$ transients. *Circulation Research*, 85(6), 515–523.
- Mauban, J. R., Zacharia, J., Fairfax, S., & Wier, W. G. (2015). PC-PLC/sphingomyelin synthase activity plays a central role in the development of myogenic tone in murine resistance arteries. *American Journal of Physiology. Heart and Circulatory Physiology*, 308(12), H1517–H1524. <http://dx.doi.org/10.1152/ajpheart.00594.2014>.
- McCarron, J. G., Olson, M. L., Wilson, C., Sandison, M. E., & Chalmers, S. (2013). Examining the role of mitochondria in $Ca(2)(+)$ signaling in native vascular smooth muscle. *Microcirculation*, 20(4), 317–329. <http://dx.doi.org/10.1111/micc.12039>.
- Meents, J. E., Neeb, L., & Reuter, U. (2010). TRPV1 in migraine pathophysiology. *Trends in Molecular Medicine*, 16(4), 153–159. <http://dx.doi.org/10.1016/j.molmed.2010.02.004>.
- Mercado, J., Baylie, R., Navedo, M. F., Yuan, C., Scott, J. D., Nelson, M. T., ... Santana, L. F. (2014). Local control of TRPV4 channels by AKAP150-targeted PKC in arterial smooth muscle. *Journal of General Physiology*, 143(5), 559–575. <http://dx.doi.org/10.1085/jgp.201311050>.
- Moosmang, S., Schulla, V., Welling, A., Feil, R., Feil, S., Wegener, J. W., ... Klugbauer, N. (2003). Dominant role of smooth muscle L-type calcium channel Cav1.2 for blood pressure regulation. *EMBO Journal*, 22(22), 6027–6034.
- Mufti, R. E., Brett, S. E., Tran, C. H., Abd El-Rahman, R., Anfinogenova, Y., El-Yazbi, A., ... Welsh, D. G. (2010). Intravascular pressure augments cerebral arterial constriction by inducing voltage-insensitive Ca^{2+} waves. *Journal of Physiology*, 588(Pt. 20), 3983–4005. <http://dx.doi.org/10.1113/jphysiol.2010.193300>.
- Mufti, R. E., Zechariah, A., Sancho, M., Mazumdar, N., Brett, S. E., & Welsh, D. G. (2015). Implications of $\alpha_v\beta_3$ integrin signaling in the regulation of Ca^{2+} waves and myogenic tone in cerebral arteries. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 35(12), 2571–2578. <http://dx.doi.org/10.1161/ATVBAHA.115.305619>.

- Muik, M., Frischauf, I., Derler, I., Fahrner, M., Bergsmann, J., Eder, P., ... Romanin, C. (2008). Dynamic coupling of the putative coiled-coil domain of ORAI1 with STIM1 mediates ORAI1 channel activation. *Journal of Biological Chemistry*, 283(12), 8014–8022. <http://dx.doi.org/10.1074/jbc.M708898200>.
- Mullins, F. M., Park, C. Y., Dolmetsch, R. E., & Lewis, R. S. (2009). STIM1 and calmodulin interact with Orai1 to induce Ca²⁺-dependent inactivation of CRAC channels. *Proceedings of the National Academy of Sciences of the United States of America*, 106(36), 15495–15500. <http://dx.doi.org/10.1073/pnas.0906781106>.
- Muraki, K., Iwata, Y., Katanosaka, Y., Ito, T., Ohya, S., Shigekawa, M., & Imaizumi, Y. (2003). TRPV2 is a component of osmotically sensitive cation channels in murine aortic myocytes. *Circulation Research*, 93(9), 829–838. <http://dx.doi.org/10.1161/01.RES.0000097263.10220.0C>.
- Narayanan, D., Adebisi, A., & Jaggar, J. H. (2012). Inositol trisphosphate receptors in smooth muscle cells. *American Journal of Physiology. Heart and Circulatory Physiology*, 302(11), H2190–H2210. <http://dx.doi.org/10.1152/ajpheart.01146.2011>.
- Narayanan, D., Bulley, S., Leo, M. D., Burris, S. K., Gabrick, K. S., Boop, F. A., & Jaggar, J. H. (2013). Smooth muscle cell transient receptor potential polycystin-2 (TRPP2) channels contribute to the myogenic response in cerebral arteries. *Journal of Physiology*, 591(Pt. 20), 5031–5046. <http://dx.doi.org/10.1113/jphysiol.2013.258319>.
- Narayanan, D., Xi, Q., Pfeffer, L. M., & Jaggar, J. H. (2010). Mitochondria control functional CaV1.2 expression in smooth muscle cells of cerebral arteries. *Circulation Research*, 107(5), 631–641. <http://dx.doi.org/10.1161/CIRCRESAHA.110.224345>.
- Navedo, M. F., & Amberg, G. C. (2013). Local regulation of L-type Ca²⁺ channel sparklets in arterial smooth muscle. *Microcirculation*, 20(4), 290–298. <http://dx.doi.org/10.1111/micc.12021>.
- Navedo, M. F., Amberg, G. C., Nieves, M., Molkentin, J. D., & Santana, L. F. (2006). Mechanisms underlying heterogeneous Ca²⁺ sparklet activity in arterial smooth muscle. *Journal of General Physiology*, 127(6), 611–622.
- Navedo, M. F., Amberg, G., Votaw, S. V., & Santana, L. F. (2005). Constitutively active L-type Ca²⁺ channels. *Proceedings of the National Academy of Sciences of the United States of America*, 102(31), 11112–11117.
- Navedo, M. F., Cheng, E. P., Yuan, C., Votaw, S., Molkentin, J. D., Scott, J. D., & Santana, L. F. (2010). Increased coupled gating of L-type Ca²⁺ channels during hypertension and Timothy syndrome. *Circulation Research*, 106(4), 748–756. <http://dx.doi.org/10.1161/CIRCRESAHA.109.213363>.
- Navedo, M. F., Nieves-Cintrón, M., Amberg, G. C., Yuan, C., Votaw, S., Lederer, W. J., ... Santana, L. F. (2008). AKAP150 is required for stuttering persistent Ca²⁺ sparklets and angiotensin II-induced hypertension. *Circulation Research*, 102(2), e1–e11. <http://dx.doi.org/10.1161/CIRCRESAHA.107.167809>. CIRCRESAHA.107.167809 [pii].
- Navedo, M. F., & Santana, L. F. (2013). CaV1.2 sparklets in heart and vascular smooth muscle. *Journal of Molecular and Cellular Cardiology*, 58, 67–76. <http://dx.doi.org/10.1016/j.yjmcc.2012.11.018>.
- Navedo, M. F., Takeda, Y., Nieves-Cintrón, M., Molkentin, J. D., & Santana, L. F. (2010). Elevated Ca²⁺ sparklet activity during acute hyperglycemia and diabetes in cerebral arterial smooth muscle cells. *American Journal of Physiology. Cell Physiology*, 298(2), C211–C220. <http://dx.doi.org/10.1152/ajpcell.00267.2009>.
- Nelson, M. T., Cheng, H., Rubart, M., Santana, L. F., Bonev, A. D., Knot, H. J., & Lederer, W. J. (1995). Relaxation of arterial smooth muscle by calcium sparks. *Science*, 270(5236), 633–637.
- Nelson, M. T., Patlak, J. B., Worley, J. F., & Standen, N. B. (1990). Calcium channels, potassium channels, and voltage dependence of arterial smooth muscle tone. *American Journal of Physiology*, 259(1 Pt. 1), C3–C18.

- Newton, C. L., Mignery, G. A., & Sudhof, T. C. (1994). Co-expression in vertebrate tissues and cell lines of multiple inositol 1,4,5-trisphosphate (InsP3) receptors with distinct affinities for InsP3. *Journal of Biological Chemistry*, 269(46), 28613–28619.
- Nieves-Cintrón, M., Amberg, G. C., Navedo, M. F., Molkentin, J. D., & Santana, L. F. (2008). The control of Ca²⁺ influx and NFATc3 signaling in arterial smooth muscle during hypertension. *Proceedings of the National Academy of Sciences of the United States of America*, 105(40), 15623–15628. <http://dx.doi.org/10.1073/pnas.0808759105>. 0808759105 [pii].
- Nieves-Cintrón, M., Amberg, G. C., Nichols, C. B., Molkentin, J. D., & Santana, L. F. (2007). Activation of NFATc3 down-regulates the β 1 subunit of large conductance, calcium-activated K⁺ channels in arterial smooth muscle and contributes to hypertension. *Journal of Biological Chemistry*, 282(5), 3231–3240.
- Nieves-Cintrón, M., Nystoriak, M. A., Prada, M. P., Johnson, K., Fayer, W., Dell'Acqua, M. L., ... Navedo, M. F. (2015). Selective downregulation of Kv2.1 function contributes to enhanced arterial tone during diabetes. *Journal of Biological Chemistry*, 290(12), 7918–7929.
- Nikitina, E., Jahromi, B. S., Bouryi, V. A., Takahashi, M., Xie, A., Zhang, Z. D., & Macdonald, R. L. (2006). Voltage-dependent calcium channels of dog basilar artery. *The Journal of Physiology*, 580, 523–541.
- Nixon, G. F., Mignery, G. A., & Somlyo, A. V. (1994). Immunogold localization of inositol 1,4,5-trisphosphate receptors and characterization of ultrastructural features of the sarcoplasmic reticulum in phasic and tonic smooth muscle. *Journal of Muscle Research and Cell Motility*, 15(6), 682–700.
- Nystoriak, M. A., Murakami, K., Penar, P. L., & Wellman, G. C. (2009). Ca(v)1.2 splice variant with exon 9* is critical for regulation of cerebral artery diameter. *American Journal of Physiology. Heart and Circulatory Physiology*, 297(5), H1820–H1828. <http://dx.doi.org/10.1152/ajpheart.00326.2009>.
- Nystoriak, M. A., Nieves-Cintrón, M., & Navedo, M. F. (2013). Capturing single L-type Ca(2+) channel function with optics. *Biochimica et Biophysica Acta*, 1833(7), 1657–1664. <http://dx.doi.org/10.1016/j.bbamcr.2012.10.027>.
- Nystoriak, M. A., Nieves-Cintrón, M., Nygren, P. J., Hinke, S. A., Nichols, C. B., Chen, C. Y., ... Navedo, M. F. (2014). AKAP150 contributes to enhanced vascular tone by facilitating large-conductance Ca²⁺-activated K⁺ channel remodeling in hyperglycemia and diabetes mellitus. *Circulation Research*, 114(4), 607–615. <http://dx.doi.org/10.1161/CIRCRESAHA.114.302168>.
- Oancea, E., Wolfe, J. T., & Clapham, D. E. (2006). Functional TRPM7 channels accumulate at the plasma membrane in response to fluid flow. *Circulation Research*, 98(2), 245–253. <http://dx.doi.org/10.1161/01.RES.0000200179.29375.cc>.
- Olah, Z., Szabo, T., Karai, L., Hough, C., Fields, R. D., Caudle, R. M., ... Iadarola, M. J. (2001). Ligand-induced dynamic membrane changes and cell deletion conferred by vanilloid receptor 1. *Journal of Biological Chemistry*, 276(14), 11021–11030. <http://dx.doi.org/10.1074/jbc.M008392200>.
- Olson, M. L., Chalmers, S., & McCarron, J. G. (2010). Mitochondrial Ca²⁺ uptake increases Ca²⁺ release from inositol 1,4,5-trisphosphate receptor clusters in smooth muscle cells. *Journal of Biological Chemistry*, 285(3), 2040–2050. <http://dx.doi.org/10.1074/jbc.M109.027094>.
- Park, C. Y., Shcheglovitov, A., & Dolmetsch, R. (2010). The CRAC channel activator STIM1 binds and inhibits L-type voltage-gated calcium channels. *Science*, 330(6000), 101–105. <http://dx.doi.org/10.1126/science.1191027>.
- Parker, I., & Smith, I. F. (2010). Recording single-channel activity of inositol trisphosphate receptors in intact cells with a microscope, not a patch clamp. *Journal of General Physiology*, 136(2), 119–127. <http://dx.doi.org/10.1085/jgp.200910390>.

- Perez, G. J., Bonev, A. D., Patlak, J. B., & Nelson, M. T. (1999). Functional coupling of ryanodine receptors to KCa channels in smooth muscle cells from rat cerebral arteries. *Journal of General Physiology*, 113(2), 229–238.
- Perez-Reyes, E. (2006). Molecular characterization of T-type calcium channels. *Cell Calcium*, 40(2), 89–96. <http://dx.doi.org/10.1016/j.ceca.2006.04.012>.
- Picard, C., McCarl, C. A., Papolos, A., Khalil, S., Luthy, K., Hivroz, C., ... Feske, S. (2009). STIM1 mutation associated with a syndrome of immunodeficiency and autoimmunity. *New England Journal of Medicine*, 360(19), 1971–1980. <http://dx.doi.org/10.1056/NEJMoa0900082>.
- Potier, M., Gonzalez, J. C., Motiani, R. K., Abdullaev, I. F., Bisailon, J. M., Singer, H. A., & Trebak, M. (2009). Evidence for STIM1- and Orai1-dependent store-operated calcium influx through ICRAC in vascular smooth muscle cells: Role in proliferation and migration. *FASEB Journal*, 23(8), 2425–2437. <http://dx.doi.org/10.1096/fj.09-131128>.
- Prakriya, M., & Lewis, R. S. (2001). Potentiation and inhibition of Ca(2+) release-activated Ca(2+) channels by 2-aminoethyldiphenyl borate (2-APB) occurs independently of IP(3) receptors. *Journal of Physiology*, 536(Pt. 1), 3–19.
- Putney, J. W., Jr. (1986). A model for receptor-regulated calcium entry. *Cell Calcium*, 7(1), 1–12.
- Reading, S. A., Earley, S., Waldron, B. J., Welsh, D. G., & Brayden, J. E. (2005). TRPC3 mediates pyrimidine receptor-induced depolarization of cerebral arteries. *American Journal of Physiology. Heart and Circulatory Physiology*, 288(5), H2055–H2061.
- Roos, J., DiGregorio, P. J., Yeromin, A. V., Ohlsen, K., Lioudyno, M., Zhang, S., ... Stauderman, K. A. (2005). STIM1, an essential and conserved component of store-operated Ca2+ channel function. *Journal of Cell Biology*, 169(3), 435–445. <http://dx.doi.org/10.1083/jcb.200502019>.
- Sabourin, J., Lamiche, C., Vandebrout, A., Magaud, C., Rivet, J., Cognard, C., ... Constantin, B. (2009). Regulation of TRPC1 and TRPC4 cation channels requires an alpha1-syntrophin-dependent complex in skeletal mouse myotubes. *Journal of Biological Chemistry*, 284(52), 36248–36261. <http://dx.doi.org/10.1074/jbc.M109.012872>.
- Saleh, S. N., Albert, A. P., & Large, W. A. (2009). Activation of native TRPC1/C5/C6 channels by endothelin-1 is mediated by both PIP3 and PIP2 in rabbit coronary artery myocytes. *Journal of Physiology*, 587(Pt. 22), 5361–5375. <http://dx.doi.org/10.1113/jphysiol.2009.180331>.
- Saleh, S. N., Albert, A. P., Peppiatt, C. M., & Large, W. A. (2006). Angiotensin II activates two cation conductances with distinct TRPC1 and TRPC6 channel properties in rabbit mesenteric artery myocytes. *Journal of Physiology*, 577(Pt. 2), 479–495. <http://dx.doi.org/10.1113/jphysiol.2006.119305>.
- Saleh, S. N., & Greenwood, I. A. (2005). Activation of chloride currents in murine portal vein smooth muscle cells by membrane depolarization involves intracellular calcium release. *American Journal of Physiology. Cell Physiology*, 288(1), C122–C131. <http://dx.doi.org/10.1152/ajpcell.00384.2004>.
- Samso, M., Wagenknecht, T., & Allen, P. D. (2005). Internal structure and visualization of transmembrane domains of the RyR1 calcium release channel by cryo-EM. *Nature Structural & Molecular Biology*, 12(6), 539–544. <http://dx.doi.org/10.1038/nsmb938>.
- Santana, L. F., & Navedo, M. F. (2009). Molecular and biophysical mechanisms of Ca2+ sparklets in smooth muscle. *Journal of Molecular and Cellular Cardiology*, 47(4), 436–444. <http://dx.doi.org/10.1016/j.yjmcc.2009.07.008>. S0022-2828(09)00279-X [pii].
- Santana, L. F., Navedo, M. F., Amberg, G. C., Nieves-Cintrón, M., Votaw, V. S., & Ufret-Vincenty, C. A. (2008). Calcium sparklets in arterial smooth muscle. *Clinical and Experimental Pharmacology & Physiology*, 35(9), 1121–1126. <http://dx.doi.org/10.1111/j.1440-1681.2007.04867.x>. CEP4867 [pii].

- Searls, Y. M., Loganathan, R., Smirnova, I. V., & Stehno-Bittel, L. (2010). Intracellular Ca^{2+} + regulating proteins in vascular smooth muscle cells are altered with type 1 diabetes due to the direct effects of hyperglycemia. *Cardiovascular Diabetology*, 9, 8. <http://dx.doi.org/10.1186/1475-2840-9-8>.
- Serysheva, I. I., Ludtke, S. J., Baker, M. L., Cong, Y., Topf, M., Eramian, D., ... Chiu, W. (2008). Subnanometer-resolution electron cryomicroscopy-based domain models for the cytoplasmic region of skeletal muscle RyR channel. *Proceedings of the National Academy of Sciences of the United States of America*, 105(28), 9610–9615. <http://dx.doi.org/10.1073/pnas.0803189105>.
- Sharif-Naeini, R., Folgering, J. H., Bichet, D., Duprat, F., Lauritzen, I., Arhatte, M., ... Honore, E. (2009). Polycystin-1 and -2 dosage regulates pressure sensing. *Cell*, 139(3), 587–596. <http://dx.doi.org/10.1016/j.cell.2009.08.045>.
- Somlyo, A. P. (1985). Excitation-contraction coupling and the ultrastructure of smooth muscle. *Circulation Research*, 57(4), 497–507.
- Spassova, M. A., Soboloff, J., He, L. P., Xu, W., Dziadek, M. A., & Gill, D. L. (2006). STIM1 has a plasma membrane role in the activation of store-operated Ca^{2+} channels. *Proceedings of the National Academy of Sciences of the United States of America*, 103(11), 4040–4045. <http://dx.doi.org/10.1073/pnas.0510050103>.
- Storch, U., Forst, A. L., Philipp, M., Gudermann, T., & Mederos y Schnitzler, M. (2012). Transient receptor potential channel 1 (TRPC1) reduces calcium permeability in heteromeric channel complexes. *Journal of Biological Chemistry*, 287(5), 3530–3540. <http://dx.doi.org/10.1074/jbc.M111.283218>.
- Strubing, C., Krapivinsky, G., Krapivinsky, L., & Clapham, D. E. (2001). TRPC1 and TRPC5 form a novel cation channel in mammalian brain. *Neuron*, 29(3), 645–655.
- Takeda, Y., Nystoriak, M. A., Nieves-Cintrón, M., Santana, L. F., & Navedo, M. F. (2011). Relationship between Ca^{2+} sparklets and sarcoplasmic reticulum Ca^{2+} load and release in rat cerebral arterial smooth muscle. *American Journal of Physiology. Heart and Circulatory Physiology*, 301(6), H2285–H2294. <http://dx.doi.org/10.1152/ajpheart.00488.2011>.
- Tasker, P. N., Michelangeli, F., & Nixon, G. F. (1999). Expression and distribution of the type 1 and type 3 inositol 1,4,5-trisphosphate receptor in developing vascular smooth muscle. *Circulation Research*, 84(5), 536–542.
- Tasker, P. N., Taylor, C. W., & Nixon, G. F. (2000). Expression and distribution of InsP(3) receptor subtypes in proliferating vascular smooth muscle cells. *Biochemical and Biophysical Research Communications*, 273(3), 907–912. <http://dx.doi.org/10.1006/bbrc.2000.3036>.
- Toth, A., Czikora, A., Pasztor, E. T., Dienes, B., Bai, P., Csernoch, L., ... Boczan, J. (2014). Vanilloid receptor-1 (TRPV1) expression and function in the vasculature of the rat. *Journal of Histochemistry and Cytochemistry*, 62(2), 129–144. <http://dx.doi.org/10.1369/0022155413513589>.
- Tovey, S. C., de Smet, P., Lipp, P., Thomas, D., Young, K. W., Missiaen, L., ... Bootman, M. D. (2001). Calcium puffs are generic InsP(3)-activated elementary calcium signals and are downregulated by prolonged hormonal stimulation to inhibit cellular calcium responses. *Journal of Cell Science*, 114(Pt. 22), 3979–3989.
- Vaithianathan, T., Narayanan, D., Asuncion-Chin, M. T., Jeyakumar, L. H., Liu, J., Fleischer, S., ... Dopico, A. M. (2010). Subtype identification and functional characterization of ryanodine receptors in rat cerebral artery myocytes. *American Journal of Physiology. Cell Physiology*, 299(2), C264–C278. <http://dx.doi.org/10.1152/ajpcell.00318.2009>.
- VanBavel, E., Sorop, O., Andreasen, D., Pfaffendorf, M., & Jensen, B. L. (2002). Role of T-type calcium channels in myogenic tone of skeletal muscle resistance arteries. *American Journal of Physiology. Heart and Circulatory Physiology*, 283(6), H2239–H2243. <http://dx.doi.org/10.1152/ajpheart.00531.2002>.

- Varga-Szabo, D., Authi, K. S., Braun, A., Bender, M., Ambily, A., Hassock, S. R., ... Nieswandt, B. (2008). Store-operated $\text{Ca}(2+)$ entry in platelets occurs independently of transient receptor potential (TRP) C1. *Pflügers Archiv*, 457(2), 377–387. <http://dx.doi.org/10.1007/s00424-008-0531-4>.
- Walker, R. L., Hume, J. R., & Horowitz, B. (2001). Differential expression and alternative splicing of TRP channel genes in smooth muscles. *American Journal of Physiology. Cell Physiology*, 280(5), C1184–C1192.
- Wang, Y., Chen, J., Wang, Y., Taylor, C. W., Hirata, Y., Hagiwara, H., ... Sakaki, Y. (2001). Crucial role of type 1, but not type 3, inositol 1,4,5-trisphosphate ($\text{IP}(3)$) receptors in $\text{IP}(3)$ -induced $\text{Ca}(2+)$ release, capacitative $\text{Ca}(2+)$ entry, and proliferation of A7r5 vascular smooth muscle cells. *Circulation Research*, 88(2), 202–209.
- Wang, Y., Deng, X., Mancarella, S., Hendron, E., Eguchi, S., Soboloff, J., ... Gill, D. L. (2010). The calcium store sensor, STIM1, reciprocally controls Orai and $\text{CaV}1.2$ channels. *Science*, 330(6000), 105–109. <http://dx.doi.org/10.1126/science.1191086>.
- Wang, Q., Hogg, R. C., & Large, W. A. (1992). Properties of spontaneous inward currents recorded in smooth muscle cells isolated from the rabbit portal vein. *Journal of Physiology*, 451, 525–537.
- Weiss, S., & Dascal, N. (2015). Molecular aspects of modulation of L-type calcium channels by protein kinase C. *Current Molecular Pharmacology*, 8(1), 43–53.
- Welsh, D. G., Morielli, A. D., Nelson, M. T., & Brayden, J. E. (2002). Transient receptor potential channels regulate myogenic tone of resistance arteries. *Circulation Research*, 90(3), 248–250.
- Welsh, D. G., Nelson, M. T., Eckman, D. M., & Brayden, J. E. (2000). Swelling-activated cation channels mediate depolarization of rat cerebrovascular smooth muscle by hyposmolarity and intravascular pressure. *Journal of Physiology*, 527(Pt. 1), 139–148.
- Wheeler, D. G., Groth, R. D., Ma, H., Barrett, C. F., Owen, S. F., Safa, P., & Tsien, R. W. (2012). $\text{Ca}(V)1$ and $\text{Ca}(V)2$ channels engage distinct modes of $\text{Ca}(2+)$ signaling to control CREB-dependent gene expression. *Cell*, 149(5), 1112–1124. <http://dx.doi.org/10.1016/j.cell.2012.03.041>.
- Wijetunge, S., & Hughes, A. D. (2007). Src family tyrosine kinases mediate contraction of rat isolated tail arteries in response to a hyposmotic stimulus. *Journal of Hypertension*, 25(9), 1871–1878. <http://dx.doi.org/10.1097/HJH.0b013e328255e8f0>.
- Wilkerson, M. K., Heppner, T. J., Bonev, A. D., & Nelson, M. T. (2006). Inositol trisphosphate receptor calcium release is required for cerebral artery smooth muscle cell proliferation. *American Journal of Physiology. Heart and Circulatory Physiology*, 290(1), H240–H247. <http://dx.doi.org/10.1152/ajpheart.01191.2004>.
- Wojcikiewicz, R. J., & Luo, S. G. (1998). Differences among type I, II, and III inositol 1,4,5-trisphosphate receptors in ligand-binding affinity influence the sensitivity of calcium stores to inositol-1,4,5-trisphosphate. *Molecular Pharmacology*, 53(4), 656–662.
- Wray, S., & Burdya, T. (2010). Sarcoplasmic reticulum function in smooth muscle. *Physiological Reviews*, 90(1), 113–178. <http://dx.doi.org/10.1152/physrev.00018.2008>.
- Xi, Q., Adebisi, A., Zhao, G., Chapman, K. E., Waters, C. M., Hassid, A., & Jaggar, J. H. (2008). IP_3 constricts cerebral arteries via IP_3 receptor-mediated TRPC3 channel activation and independently of sarcoplasmic reticulum Ca^{2+} release. *Circulation Research*, 102(9), 1118–1126. <http://dx.doi.org/10.1161/CIRCRESAHA.108.173948>.
- Xi, Q., Cheranov, S. Y., & Jaggar, J. H. (2005). Mitochondria-derived reactive oxygen species dilate cerebral arteries by activating Ca^{2+} sparks. *Circulation Research*, 97(4), 354–362. <http://dx.doi.org/10.1161/01.RES.0000177669.29525.78>.
- Xu, S. Z., Boulay, G., Flemming, R., & Beech, D. J. (2006). E3-targeted anti-TRPC5 antibody inhibits store-operated calcium entry in freshly isolated pial arterioles. *American Journal of Physiology. Heart and Circulatory Physiology*, 291(6), H2653–H2659. <http://dx.doi.org/10.1152/ajpheart.00495.2006>.

- Zacharia, J., Zhang, J., & Wier, W. G. (2007). Ca^{2+} signaling in mouse mesenteric small arteries: Myogenic tone and adrenergic vasoconstriction. *American Journal of Physiology. Heart and Circulatory Physiology*, 292(3), H1523–H1532. <http://dx.doi.org/10.1152/ajpheart.00670.2006>.
- Zalk, R., Clarke, O. B., des Georges, A., Grassucci, R. A., Reiken, S., Mancina, F., ... Marks, A. R. (2015). Structure of a mammalian ryanodine receptor. *Nature*, 517(7532), 44–49. <http://dx.doi.org/10.1038/nature13950>.
- Zhang, W., Halligan, K. E., Zhang, X., Bisaillon, J. M., Gonzalez-Cobos, J. C., Motiani, R. K., ... Trebak, M. (2011). Orai1-mediated I (CRAC) is essential for neointima formation after vascular injury. *Circulation Research*, 109(5), 534–542. <http://dx.doi.org/10.1161/CIRCRESAHA.111.246777>.
- Zhang, S. L., Yu, Y., Roos, J., Kozak, J. A., Deerinck, T. J., Ellisman, M. H., ... Cahalan, M. D. (2005). STIM1 is a Ca^{2+} sensor that activates CRAC channels and migrates from the Ca^{2+} store to the plasma membrane. *Nature*, 437(7060), 902–905. <http://dx.doi.org/10.1038/nature04147>.
- Zhang, W., Zhang, X., Gonzalez-Cobos, J. C., Stolwijk, J. A., Matrougui, K., & Trebak, M. (2015). Leukotriene-C4 synthase, a critical enzyme in the activation of store-independent Orai1/Orai3 channels, is required for neointimal hyperplasia. *Journal of Biological Chemistry*, 290(8), 5015–5027. <http://dx.doi.org/10.1074/jbc.M114.625822>.
- Zhao, G., Adebiyi, A., Blaskova, E., Xi, Q., & Jaggar, J. H. (2008). Type 1 inositol 1,4,5-trisphosphate receptors mediate UTP-induced cation currents, Ca^{2+} signals, and vasoconstriction in cerebral arteries. *American Journal of Physiology. Cell Physiology*, 295(5), C1376–C1384. <http://dx.doi.org/10.1152/ajpcell.00362.2008>.
- Zhao, G., Neeb, Z. P., Leo, M. D., Pachuau, J., Adebiyi, A., Ouyang, K., ... Jaggar, J. H. (2010). Type 1 IP₃ receptors activate BKCa channels via local molecular coupling in arterial smooth muscle cells. *Journal of General Physiology*, 136(3), 283–291. <http://dx.doi.org/10.1085/jgp.201010453>.
- Zhou, H., Nakamura, T., Matsumoto, N., Hisatsune, C., Mizutani, A., Iesaki, T., ... Mikoshiba, K. (2008). Predominant role of type 1 IP₃ receptor in aortic vascular muscle contraction. *Biochemical and Biophysical Research Communications*, 369(1), 213–219. <http://dx.doi.org/10.1016/j.bbrc.2007.12.194>.