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The Calcium Signaling Mechanisms in Arterial Smooth Muscle and Endothelial Cells

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Abstract

The contractile state of resistance arteries and arterioles is a crucial determinant of blood pressure and blood flow. Physiological regulation of arterial contractility requires constant communication between endothelial and smooth muscle cells. Various Ca^{2+} signals and Ca^{2+}-sensitive targets ensure dynamic control of intercellular communications in the vascular wall. The functional effect of a Ca^{2+} signal on arterial contractility depends on the type of Ca^{2+}-sensitive target engaged by that signal. Recent studies using advanced imaging methods have identified the spatiotemporal signatures of individual Ca^{2+} signals that control arterial and arteriolar contractility. Broadly speaking, intracellular Ca^{2+} is increased by ion channels and transporters on the plasma membrane and endoplasmic reticular membrane. Physiological roles for many vascular Ca^{2+} signals have already been confirmed, while further investigation is needed for other Ca^{2+} signals. This article focuses on endothelial and smooth muscle Ca^{2+} signaling mechanisms in resistance arteries and arterioles. We discuss the Ca^{2+} entry pathways at the plasma membrane, Ca^{2+} release signals from the intracellular stores, the functional and physiological relevance of Ca^{2+} signals, and their regulatory mechanisms. Finally, we describe the contribution of abnormal endothelial and smooth muscle Ca^{2+} signals to the pathogenesis of vascular disorders.

Introduction

Vascular resistance is a crucial determinant of blood pressure and blood flow to target organs. The contractile state of small arteries and arterioles determines vascular resistance. Smooth muscle cells (SMCs) and endothelial cells (ECs) are the two main cell-types involved in the dynamic regulation of vascular contractility. Both SMCs and ECs recruit various Ca^{2+} signaling mechanisms to regulate vascular contractility (Figure 1) (344). The canonical view is that endothelial and SMC Ca^{2+} have opposite effects on vascular diameter. While increases in endothelial Ca^{2+} cause vasodilation, increases in SMC Ca^{2+} have mostly been linked to vasoconstriction, except for Ca^{2+} sparks (Table 1), which can cause

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vasodilation. Moreover, intracellular Ca^{2+} plays a central role in EC-SMC communication, which is pivotal for physiological regulation of vascular contractility.

Cytosolic Ca^{2+} levels can increase via the influx of extracellular Ca^{2+} or release of Ca^{2+} from intracellular stores, including endoplasmic reticulum (ER) or sarcoplasmic reticulum (SR) and lysosomes. The majority of Ca^{2+} signals in the arteriolar walls occur in a spatially restricted manner, with the diffusion of Ca^{2+} limited by numerous Ca^{2+}-binding proteins and high viscosity of the cytosol. The spatially restricted nature of Ca^{2+} signals confers the specificity of targets/functional effects and limits toxicity to the cell. Moreover, signaling microdomains that localize Ca^{2+} signals with their signaling targets ensure specific activation of the targets. Such signaling microdomains also provide efficient Ca^{2+} signal-target coupling, whereby smaller increases in Ca^{2+} can activate a small number of nearby target molecules to achieve physiological effects. EC projections to SMCs, or myoendothelial projections (MEPs), are prime examples of signaling microdomains enabled by specialized microstructures. The majority of endothelial Ca^{2+} signals occur at MEPs, and Ca^{2+}-sensitive targets also localize to MEPs. The Ca^{2+} signal-target proximity at MEPs facilitates efficient and precise communication between ECs and SMCs. Similarly, signaling nanodomains involving localization of proteins inside the caveolae have been shown in ECs and SMCs. In SMCs, signaling microdomains are enabled by structural features (e.g., proximity of the SR to the membrane) or co-localization of Ca^{2+} channels with other ion channels or anchoring proteins. In this article, we discuss the Ca^{2+} signal-target linkages in arteries and arterioles, regulatory mechanisms, and abnormalities in Ca^{2+} signaling that contribute to the pathogenesis of vascular disorders.

SMC Ca^{2+} Signals in Small Arteries and Arterioles

SMCs are the contractile cells in vascular walls. Several physiological stimuli, including intravascular pressure, G-protein coupled receptors (GPCRs), and neurohumoral mediators, contract SMCs from resistance-sized arteries. Under resting conditions, arterial contractility is mainly determined by intraluminal pressure-induced constriction (myogenic constriction) and nerve-induced (neurogenic) constriction. Myogenic vasoconstriction is an inherent feature of SMCs from resistance-sized arteries (27). It is also a crucial contributor to vascular resistance and autoregulation of blood flow (83).

Both myogenic and neurogenic vasoconstrictions are accomplished predominantly through an increase in SMC Ca^{2+}. Moreover, neurohumoral mediators can activate GPCRs on SMC membranes to increase SMC Ca^{2+}. The importance of distinguishing global versus local increases in SMC Ca^{2+} is well documented (reviewed in Ref. 344). Whole-cell increases in SMCs Ca^{2+} result in vasoconstriction. On the contrary, some localized increases in Ca^{2+} (Ca^{2+} sparks, Table 1) can cause vasodilation (305, 318, 352). The canonical pathway for SMC contraction involves Ca^{2+}-calmodulin (CaM)-dependent activation of myosin light chain kinase (MLCK). MLCK phosphorylates the myosin regulatory light chain (RLC20), initiating actin-myosin cross-bridge formation that results in SMC contraction (429). A parallel GPCR-mediated pathway activates RhoA-dependent kinase (ROCK), which phosphorylates and inhibits myosin light chain phosphatase (MLCP). MLCP inhibition results in reduced RLC20 dephosphorylation and sustained SMC contraction. Additionally,

the p90 Ribosomal S6 Kinase 2 (RSK2) has been recently proposed as an upstream mediator of Ca^{2+}-dependent and Ca^{2+}-independent SMC contraction (19). Intraluminal pressure and GPCR activation facilitated RSK2 activation via extracellular signal-regulated kinase (ERK1/2) and phosphoinositide-dependent kinase (PKD) signaling pathway. RSK2, in turn, directly phosphorylated RLC20 and activated the Na^+/H^+ exchanger causing alkalization-dependent Ca^{2+} release and SMC contraction.

Ca^{2+} influx from extracellular compartment

The cytosolic concentration of free Ca^{2+} is maintained low (~100 nM) by the presence of Ca^{2+}-binding proteins and intracellular organelles that act as storages of Ca^{2+} (72). A negatively charged intracellular environment, coupled with high extracellular Ca^{2+} concentration (~1–2 mM), accounts for an electrochemical gradient favorable for Ca^{2+} influx into the cells. The opening of Ca^{2+} permeable ion channels on the SMC membranes allows extracellular Ca^{2+} to move into the cytosol along the electrochemical gradient. The Ca^{2+} entry mechanisms on SMC membranes can be broadly divided into voltage-gated and non-voltage-gated. The voltage-gated Ca^{2+} entry pathways on SMC membranes include L-type and T-type Ca^{2+} channels and the non-voltage-gated Ca^{2+} entry mechanisms include transient receptor potential (TRP) channels, PIEZO channels, store-operated Ca^{2+} entry (SOCE), purinergic receptors, and Na^+/Ca^{2+} exchangers (NCXs).

Voltage-gated Ca^{2+} entry pathways (L-type and T-type Ca^{2+} channels)—Whole-cell patch-clamp studies on SMCs isolated from rat mesenteric arteries identified two types of Ca^{2+} currents—transient (T-type) and long-lasting (L-type) (29). The ion channels underlying T-type and L-type Ca^{2+} currents were voltage-gated, implying that a structural feature (voltage sensor) enables channel opening in response to membrane depolarization. T-type or transient Ca^{2+} channel (TTCC) currents exhibited faster inactivation properties when compared to L-type or long-lasting Ca^{2+} channel (LTCC) currents. However, this distinction can be misleading since the observed channel inactivation properties depend heavily on the experimental conditions (28). A more meaningful distinction between the two channel types can be derived from comparisons of their voltage-gating properties. TTCCs are activated at more negative voltages (−60 mV) compared to LTCCs, which are activated at more depolarized voltages (−30 mV) (331, 533). The current-voltage relationship for TTCCs shows a peak current at −15 mV whereas LTCCs show peak currents at +20 mV (108). LTCC and TTCC expression varies among different vascular beds and different-sized arteries within the same vascular bed. Western blotting experiments showed similar expression of TTCCs and LTCCs in the aorta (24). On the contrary, TTCC expression was found to be higher than LTCCs in mesenteric arteries, arterioles (24), and cerebral arteries (1, 150, 154). A definitive assessment of the relative abundance of arterial LTCCs and TTCCs may require more precise quantitative techniques such as mass spectrometry.

Structure of voltage-gated Ca^{2+} channels.: Three different families of voltage-gated Ca^{2+} channels (Ca_V1, Ca_V2, and Ca_V3) share a similar structure (107, 427). The amino acid sequence of the large pore-forming α1 subunit (~190 kDa, ~2000 amino acids) determines the gating properties and sensitivity to Ca^{2+} channel blockers (55, 460). Ten α1 subunits, encoded by ten different genes, have been identified. The α1 subunit is organized in four

(I-IV) homologous domains, each composed of six transmembrane segments (TM 1-6). A membrane-associated loop (loop P) between TM5-6 from each domain forms the channel pore. TM4 is enriched with positively charged amino acids (lysine or glycine) and has been described as the voltage-sensing domain (VSD) (180). In response to membrane depolarization, TM4 rotates and opens the channel pore. Glutamate residues on loop P confer Ca^{2+} selectivity to the channel. TM6, which lines the inner pore, is the binding site for phenylalkylamines and dihydropyridines (Ca^{2+} channel blockers). Therefore, the amino acid sequence of TM6 determines the selectivity of the Ca^{2+} channel blockers against different Ca^{2+} channel subtypes (176).

Four additional accessory subunits have been identified for LTCCs: a dimer $\alpha 2\delta$ of 170 kDa, an intracellular β subunit of approximately 55 kDa, and a TM γ subunit of 33 kDa (460). $\alpha 2\delta$ and γ subunits are type-I TM proteins. α2 subunit is localized extracellularly and bound to δ subunit by a disulfide bond (55). β subunit binds with a high affinity to the intracellular I-II linker of the α1 subunit (370). The presence of Ca^{2+} currents in a cell line overexpressing α1 subunit alone revealed that α1 subunit is sufficient to form a functional Ca^{2+} channel, albeit with altered gating properties (354). Co-expression of α1 and β subunits increased channel expression and normalized the gating properties (237), indicating an essential role for the regulatory subunits in controlling channel expression and function. Among the accessory β subunits, β3 was the principal isoform in SMCs (221). Current evidence suggests that unlike LTCCs, TTCCs are not associated with any auxiliary subunits (55).

L-type Ca^{2+} channels (LTCC).: $Ca_V1.1$-1.3 gene family encodes the α1 subunits of LTCCs. $Ca_V1.2$, encoding for α1C subunit, has been regarded as the primary voltage-gated Ca^{2+} influx pathway in SMCs (Figure 2). $Ca_V1.2$ channels are the primary mediators of myogenic vasoconstriction and vasoconstriction induced by the activation of α1-adrenergic receptors and angiotensin II receptors (128, 300). $Ca_V1.2$ channel displays a unitary conductance of approximately 25 pS with Ba^{2+} as a charge carrier (71). Ca^{2+} profoundly influences the open-state probability and inactivation kinetics of the $Ca_V1.2$ channel. The C-terminal tail of the α1 subunit contains a CaM-binding isoleucine-glutamine (IQ) domain (385). Ca^{2+}-CaM binding to the IQ domain results in the modulation of channel activity. Consistent with this property, the substitution of isoleucine with alanine in the IQ motif impaired Ca^{2+}-dependent inactivation and revealed the Ca^{2+}-dependent activation of the channel. However, the substitution of the same isoleucine with glutamate resulted in the loss of Ca^{2+}-dependent activation and inactivation of the channel (142, 357, 565). Ca^{2+}-dependent inactivation limit Ca^{2+} entry through the channel during sustained membrane depolarization and prevents Ca^{2+} overload and cytotoxicity.

Protein kinases (PKA, PKC, and PKG) are among the most important regulators of LTCC activity in SMCs (289). Nitric oxide (NO) induced cyclic guanosine monophosphate (cGMP)-PKG activation to reduce LTCC currents in SMCs, partly accounting for NO-dependent vasodilation (9, 39). Furthermore, inhibition of protein kinase G (PKG) increased LTCC activity, further supporting the inhibitory role of NO-cGMP-PKG signaling on LTCC activity in SMCs (393, 473). There are conflicting reports on PKA-modulation of LTCC activity in SMCs (218). Protein kinase A (PKA) phosphorylated Ser^{1928} on the C-tail of

α1C subunit of LTCC, potentiating channel activity (125). In SMCs from cerebral arteries, exposure to high extracellular glucose increased LTTC currents. Interestingly, glucose-induced increase in LTTC activity was mediated by PKA activation and its anchoring close to LTCCs by A-kinase anchoring protein 150 (AKAP150) (317). β Adrenergic receptor-mediated activation of PKA, however, has concentration-dependent effects on LTCC activity. Low concentrations of isoproterenol (ISO, β adrenergic receptor agonist) or forskolin (PKA activator) increased LTCC currents, whereas high concentrations of ISO or forskolin had a biphasic effect—an immediate increase in LTCC currents followed by a decrease in currents (197). Compartmentalization of cAMP/PKA signaling in AKAP150-enriched plasma membrane microdomains could explain the biphasic effects of cAMP/PKA signaling in SMCs. In this regard, PKA-dependent activation of Ca^{2+}-sensitive K^+ channels hyperpolarized the plasma membrane, thereby deactivating LTCCs (348, 366). Protein kinase C (PKC) regulates LTCC via multiple modes of action. Inhibition of PKC impaired the development of myogenic constriction in cremaster arteries (173). Still, it did not affect myogenic constriction in ophthalmic arteries (198), indicating heterogeneous effects of PKC on LTCC-dependent myogenic vasoconstriction. Among the four canonical PKC isoforms (α, βI, βII, and γ) (439), PKCα appears to be the mediator of myogenic constriction in coronary arteries (89). PKCα also increased the open-state probability of LTTCs in AKAP150-enriched microdomains on SMC membranes in cerebral arteries (314, 315). Navedo and colleagues (316) indicated that AKAP150 recruits PKCα close to LTCCs and allows spatially restricted activation of LTCCs (Ca^{2+} sparklets, Table 1). Thus, protein kinases play a crucial role in fine-tuning the activity of SMC LTCCs.

T-type Ca^{2+} channels (TTCC).: Ca_V3 (3.1–3.3) genes encode for α1G, α1H, and α1I subunits that mediate TTCC currents. TTCCs show a single-channel conductance of 7.5 to 9 pS, and similar conductance with Ba^{2+} or Ca^{2+} as a charge carrier (56). A critical structural distinction between LTCCs and TTCCs is that the TTCCs have not been associated with any auxiliary subunits (55). $Ca_V3.1$-3.3 RNA levels and expression were detected in cremaster, renal, mesenteric, and cerebral arteries (47, 141, 148, 236, 495). The majority of the studies on vascular TTCCs have used mibefradil, a non-specific TTCC inhibitor. Therefore, the importance of SMC TTCC in the development of myogenic vasoconstriction remains unclear (236, 495). In rat cerebral main basilar arteries, myogenic constriction was mostly mediated by LTCCs, whereas TTCCs were important for myogenic constriction in large and small side branches (236). Pressure myography studies in mesenteric arteries from $Ca_V3.1^{-/-}$ mice suggested a predominant role for TTCCs in the development of myogenic constriction at lower intravascular pressures (40 mmHg) and a more important role for LTCCs at higher intravascular pressures (100 mmHg) (38). Similarly, in cerebral arteries, TTCCs contributed to myogenic constriction at lower pressures (20 mmHg) and hyperpolarized membrane potential (−60 mV) (Figure 2). Computational modeling predicts that TTCCs might be playing a predominant role in facilitating myogenic vasoconstriction under resting conditions, although further studies are needed to confirm this hypothesis (1). In this regard, Harraz and colleagues (150, 152) recently linked the Ca^{2+} influx through $Ca_V3.2$ channels to the dilation of cerebral arteries (Figure 2). The authors showed that $Ca_V3.2$ channels activate ryanodine receptors (RyRs) on the SR membrane, triggering Ca^{2+} sparks (Ca^{2+} release signals from the SR, Table 1). Ca^{2+} sparks activate large-conductance,

Ca^{2+} activated potassium (BK) channels, thus initiating a negative feedback mechanism that counteracts myogenic vasoconstriction. Notably, TTCCs lack Ca^{2+}-dependent inactivation, making them an ideal source of Ca^{2+} for RyR activation and initiation of Ca^{2+} sparks via Ca^{2+}-induced Ca^{2+} release. In a recent study, this research team reported that $Ca_V3.2$ and RyRs co-localize in caveolar nanodomains, and genetic deletion of caveolin-1 disrupts $Ca_V3.2$-RyR interaction (161).

Regulation of TTCCs occurs through different cellular mechanisms. NO-dependent activation of cGMP/PKG signaling inhibited TTCC currents and TTCC-induced myogenic constriction in rat cerebral arteries (151). PKA also inhibited TTCC currents, particularly the currents through $Ca_V3.2$ isoform (155). Reactive oxygen species (ROS) have diverse effects on TTCC activity. Superoxide radicals enhanced the expression of $Ca_V3.1$ and $Ca_V3.2$ channels and their contribution to myogenic vasoconstriction in cremaster and mesenteric arteries (185). In contrast, hydrogen peroxide (H_2O_2) inhibited $Ca_V3.2$ channel currents (340). Furthermore, Ang II-dependent activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme suppressed $Ca_V3.2$ currents, thereby impairing $Ca_V3.2$-RyR-BK channel signaling and promoting vasoconstriction in response to Ang II (163).

Non-voltage-gated Ca^{2+} entry pathways (TRP channels, PIEZO channel, Purinergic Receptor, and Na^+/Ca^{2+} exchanger)—TRP channels are the primary non-voltage-gated Ca^{2+} influx pathways on SMC membranes. TRP channels participate in the regulation of SMC contractility and proliferation. These functions are achieved either by promoting global or localized increases in intracellular Ca^{2+} or by inducing the activation of ion channels that cause membrane depolarization. The mammalian family of TRP channels can be divided into six subfamilies: TRPC (Canonical), TRPM (Melastatin), TRPML (Mucolipins), TRPV (Vanilloid), TRPP (Polycystic), and TRPA (Ankyrin-rich protein). All TRP channels share the same general structure. Functional TRP channels are composed of four subunits, each subunit with six TM domains (S1-S6) and intracellular C- and N-terminal tails of variable lengths. A 25-amino acids domain named “TRP domain”, located immediately after S6 toward the C-terminal is conserved among TRPV, TRPM, and TRPC subfamilies but is not found in TRPA1, TRPP, and TRPML channels (378). TRP domain is the binding site for phosphatidylinositol 4,5-bisphosphate (PIP2) (456). PIP2 modulation of TRP channels is complex and may result in channel inhibition or activation depending on the channel and experimental conditions (388). TRPV, TRPA, and TRPC channels exhibit multiple Ankyrin repeat domains (ARDs) on the N-terminal tail that contribute to channel regulation via protein-protein interactions (98). ARD3 is essential for the physical assembly of the functional tetrameric structure of TRPV5 and TRPV6 channels (106). While TRPV1 and TRPV4 channel activity is enhanced by adenosine triphosphate (ATP) binding to the concave surface located between ARD1-3 (260), TRPV3 channels sensitization is prevented following ATP binding to ARD1-3 (358). Ca^{2+}-CaM binding site at the C-terminal tail is responsible for the modulation of TRP channel activity by cytosolic Ca^{2+}, an essential regulator of TRP channel activity (159, 560, 562). Additionally, a Ca^{2+}-CaM binding site within the TRP domain has also been shown for the TRPV family (135).

TRPV (TRPV1 and TRPV4) channels.: High unitary conductance and permeability for Ca^{2+} are characteristic properties of TRPV channels. TRPV channels show a range of selectivity for Ca^{2+}, although most TRPV channels are more selective for Ca^{2+} over Na^{+}. Among the TRPV subfamily members, only TRPV1 and TRPV4 channels have been shown to be expressed in native SMCs from resistance arteries (Figure 3A) (95). TRPV1 channel has a unitary conductance of 35 to 70 pS and higher permeability for divalent over monovalent cations (P_{Ca2+}/P_{Na+} = 10) (54, 397). TRPV1 channel agonist, capsaicin, constricted canine denervated mesenteric arteries, supporting a contractile role of TRPV1 channels (365). Studies by Kark and colleagues (214) further demonstrated a vasoconstrictor role for TRPV1 channels in skeletal muscle arteries, although the cell-type containing TRPV1 channels in the vascular wall was not clear. Studies by Cavanaugh and colleagues (57) in TRPV1-LacZ reporter mouse confirmed a robust expression of TRPV1 channels in SMCs from cerebral arteries. Moreover, TRPV1 channel activation increased intracellular Ca^{2+} in SMCs, an effect that was blunted in the arteries from $TRPV1^{-/-}$ mice (57). Although the *ex vivo* findings suggest that SMC TRPV1 channels are contractile, their potential physiological role in influencing vascular resistance remains unknown. Indeed, resting blood pressure is unaltered in $TRPV1^{-/-}$ mice (280, 561). Therefore, studies in SMC specific $TRPV1^{-/-}$ mice are needed to address the physiological role of SMC TRPV1 channel.

Cytosolic Ca^{2+}, PKC, and calcineurin are the main endogenous regulators of TRPV1 channel activity (361). TRPV1 channel current is inhibited by physiological Ca^{2+} concentrations (397). Ca^{2+}-CaM dependent decrease in TRPV1 channel currents was prevented by deleting a 35-amino acids sequence (Glu^{767}-Thr^{801}) on the C-terminal tail of the TRPV1 channel (333). PKC-dependent phosphorylation of Ser^{502}, Thr^{704}, and Ser^{800} activated TRPV1 channels (334, 507), whereas calcineurin-dependent dephosphorylation inhibited channel activity (265).

SMC TRPV4 channels have been variously reported to cause dilation or constriction depending on the signaling targets they activate and the vascular bed under consideration. The unitary conductances of TRPV4 channels are 50 to 60 pS at −60 mV, and 90 to 100 pS at +60 mV (441, 511, 512). TRPV4 channels display higher permeability for Ca^{2+} over Na^{+} (P_{Ca2+}/P_{Na+} = 6–10) (85, 501), and can be activated by temperature, mechanical stimuli, and neurohumoral mediators. In SMCs from cerebral arteries, Ca^{2+} influx through TRPV4 channels (Table 1) promoted vasodilation. Ca^{2+} influx through TRPV4 channels increased the activity of RyR-BK channel signaling, hyperpolarizing SMC by approximately 10 mV and causing vasodilation (Figure 3B) (96). A similar mechanism was described in resistance mesenteric arteries and was shown to be impaired in $TRPV4^{-/-}$ mice (101). SMC TRPV4 channels appear to play a pivotal role in counteracting Ang II-induced vasoconstriction in cerebral arteries. Mercado and colleagues (292) indicated that Ang II enhances SMC TRPV4 channel activity in cerebral arteries via AKAP150 anchoring of PKCα close to TRPV4 channels and subsequent channel phosphorylation. Indeed, Ang II signaling increased the proximity between AKAP150 and TRPV4 channels. Superresolution nanoscopic studies showed that TRPV4 channel activation by Ang II decreases exponentially with the distance between AKAP150 and TRPV4 channel. TRPV4 channel activity was undetectable if AKAP150 and TRPV4 channel are more than 200 nm apart. Interestingly, the distance

between AKAP150 and TRPV4 channel, and the role of TRPV4 channel in counteracting Ang II-dependent vasoconstriction were variable among different vascular beds (459). TRPV4 channels are also expressed in SMCs from pulmonary arteries (281). In chronic hypoxia, TRPV4 channel is upregulated in mice pulmonary arteries resulting in higher contractility and a pulmonary hypertensive phenotype (528, 538). Thus, SMC TRPV4 channels appear to have distinct effects on vascular diameter in systemic and pulmonary arteries.

Several endogenous regulators of TRPV4 channel activity have been identified. Cytosolic Ca^{2+} has a biphasic effect on TRPV4 channel activity. Low concentrations of intracellular Ca^{2+} facilitate TRPV4 channel opening, whereas high concentrations limit the channel activity. Ca^{2+}-dependent activation/inactivation of TRPV4 channels occurs via Ca^{2+}-CaM binding on the C-terminal tail (C-CaMB) of the channel (362, 442, 510). Half-maximal CaM binding affinity at C-CaMB was observed at nanomolar concentrations of Ca^{2+} (150 nM). Mutations in C-CaMB resulted in the impairment of Ca^{2+}-dependent potentiation of TRPV4 channel activity (442). Notably, Ca^{2+}-dependent inhibition of the TRPV4 channel at a higher concentration of Ca^{2+} (IC_{50} of 406 nM) was maintained in the mutants (442, 510). These findings indicated that Ca^{2+}-dependent inhibition of TRPV4 channel does not rely on Ca^{2+}-CaM binding to C-CaMB. Strotmann and colleagues (443) proposed a mechanism whereby an interaction between the N- and C-terminal tails prevents channel activation. An increase in cytosolic Ca^{2+} enabled CaM binding to the C-CaMB, which resulted in the displacement of N-terminal from the C-terminal tail and TRPV4 channel activation. Recently, a Ca^{2+}-CaM binding site was identified on the N-terminal tail (aa 132–383, N-CaMB) (358). Phelps and colleagues (358) demonstrated that ATP interaction with N-CaMB increases TRPV4 channel currents. It could be speculated that at higher cytosolic Ca^{2+} concentrations, Ca^{2+}-CaM competes with ATP for binding to N-CaMB, resulting in TRPV4 channel inhibition. Such a mechanism has been proposed for Ca^{2+}-CaM-dependent TRPV1 channel inhibition (260, 389). Unfortunately, studies on Ca^{2+}-induced inactivation of the TRPV4 channel are scarce.

Protein kinases are another important endogenous regulators of TRPV4 channel activity. In expression systems, PKC augmented TRPV4 channel activity by phosphorylating Ser^{162}, Thr^{175}, and Ser^{189} on the N-terminal tail; whereas PKA increased TRPV4 channel activity by phosphorylating Ser^{824} on the C-terminal tail. Moreover, AKAP150 enhanced TRPV4 channel phosphorylation by PKA and PKC (51, 111). Epoxyeicosatrienoic acids (EETs), formed from arachidonic acid (AA) by phospholipase A2, are also known to activate TRPV4 channels (502, 511). Overall, the presence of TRPV4 channels in SMCs and their role in controlling vascular contractility are well established. However, addressing the significance of SMC TRPV4 channels at the whole-animal level awaits the development of SMC-specific $TRPV4^{-/-}$ mice.

TRPC (TRPC1/TRPC3/TRPC6) channels.: TRPC1 is a non-selective cation channel with similar permeability to Ca^{2+} and monovalent cations (P_{Na+}/P_{Ca2+} = 0.95). The unitary conductance of TRPC1 channels is approximately 5 pS (444). It is unclear whether TRPC1 monomers form a functional channel or form heteromeric structures with other TRP channels, thereby influencing their properties. TRPC1 channels have been proposed

to mediate SOCE into SMCs, although the SOCE through TRPC1 channels remains controversial (10, 30, 235, 322, 462). In SMCs from rabbit cerebral arteries, inhibiting TRPC1 channel with a specific antibody impaired thapsigargin (sarco-endoplasmic reticulum Ca^{2+}-ATPase or SERCA inhibitor)-induced increase in intracellular Ca^{2+} by approximately 20%. This result might suggest that the Ca^{2+} influx following the depletion of intracellular Ca^{2+} stores is mediated, in part, by TRPC1 channel (532). Additionally, SOCE was impaired in SMCs from mesenteric arteries of $TRPC1^{-/-}$ mice. Later studies showed that TRPC1 channel activation by depletion of Ca^{2+} stores occurs through PKC-phosphorylation of the channel, facilitating PIP2 binding and channel activation (415, 416, 504). The depletion of intracellular Ca^{2+} stores enhanced PKC activity via Gαq-dependent activation of phospholipase Cβ1 (PLCβ1) (417). However, studies in cerebral arteries by Dietrich et al. (91) suggested that TRPC1 channel is not a required element for SOCE. Furthermore, TRPC1 channels did not contribute to myogenic vasoconstriction. Saleh et al. (395) documented that in freshly isolated SMC from rabbit mesenteric artery, a high concentration of Ang II (100 nM) evokes currents inhibited by TRPC1 antibodies. In a vascular injury model, TRPC1 channel was upregulated in SMCs, resulting in enhanced Ca^{2+} entry. TRPC1 channel upregulation in this model was prevented by arresting the cell cycle (G1-S phase), indicating that TRPC1 channel may be involved in cell proliferation (234). Despite several studies on SMC TRPC1 channels, the physiological role of SMC TRPC1 channels remains a matter of debate.

The functional expression of TRPC3 channels in SMCs has also been supported by multiple studies (Figure 3A) (497). The unitary conductance for TRPC3 channel is approximately 68 pS (367). As with TRPC1 channel, the permeability of TRPC3 channel is similar for monovalent and divalent cations (P_{Ca2+}/P_{Na+} = 1.62) (210). Diacylglycerol (DAG) is a direct activator of TRPC3 channels and was found to activate the channels in a PKC-independent manner. Unlike TRPV and TRPC1 channels, PKC seemed to inhibit TRPC3 channel activity (177, 489). Conditional SMC-specific $TRPC3^{-/-}$ mice were protected against sustained seizure activity in a mouse model (81). The authors proposed that SMC TRPC3 channels mediated the seizure-induced neurovascular uncoupling and subsequent reduction in cerebral blood flow (81). In cerebral arteries, C-terminal tail of TRPC3 channel interacted with N-terminal tail of nearby inositol triphosphate receptor 1 (IP3R1) channels, resulting in TRPC3 channel activation and membrane depolarization. In turn, SMC membrane depolarization activated voltage-gated Ca^{2+} channels and caused vasoconstriction (5, 525). Future studies may use the newly generated SMC-specific $TRPC3^{-/-}$ mice (81) to unravel the physiological roles of SMC TRPC3 channel.

The third TRPC channel expressed in SMCs, TRPC6 channel (Figure 3A), shows a unitary conductance of approximately 35 pS. Importantly, TRPC6 channel is several times more permeable to bivalent cations over monovalent cations (P_{Ca2+}/P_{Na+} = 5). Intracellular Ca^{2+} has a biphasic effect of potentiation followed by inhibition on TRPC6 channels (177, 193). Similar to TRPC3 channels, TRPC6 channels are directly activated by DAG in a PKC-independent manner (177). In a recent cryo-electron microscopy (EM) study, the region between segment 6 (S6) and the pore-helix formed by adjacent subunits was proposed as the binding site for DAG (22). In a study by Cayouette and colleagues (58) in human embryonic kidney cells, Gq-protein coupled receptor (GqPCR) signaling induced the trafficking of

TRPC6 channels to the plasma membrane, resulting in increased Ca^{2+} influx. In SMCs from rat mesenteric arteries, stimulation of α1 adrenergic receptor (α1AR) and consequent PLC-DAG signaling increased TRPC6 channel currents (22). Furthermore, Ca^{2+} influx through TRPC6 channel enhanced the channel activity via Ca^{2+}-CaM-dependent protein kinase II (CaMKII)-phosphorylation of Thr^{487} on TRPC6 channel. On the contrary, chronic increases in intracellular Ca^{2+} inhibited TRPC6 channels via PKC activation (418).

Current evidence suggests that TRPC6 channels are not directly mechanosensitive, although GqPCR-activation of TRPC6 channels was shown to prime the channel for mechanosensation (192). In a separate study, Spassova et al. (435) indicated that TRPC6 channels could sense the membrane stretch, which may explain the contribution of TRPC6 channels to myogenic vasoconstriction. In SMCs from cerebral arteries of $TRPC6^{-/-}$ mice, TRPC3 channels were upregulated and myogenic vasoconstriction was shifted toward lower pressure values. The increase in vasoreactivity in $TRPC6^{-/-}$ mice raises the possibility of a heteromeric TRPC6/TRPC3 channel complex in which TRPC6 channel inhibits TRPC3 channel activity (435). On the contrary, in an earlier study, Welsh and colleagues (515) showed that acute TRPC6 channel knockdown in SMCs from cerebral arteries impaired myogenic vasoconstriction. The discrepancy between the two studies could be explained by potential compensatory upregulation of other Ca^{2+} entry pathways in the global $TRPC6^{-/-}$ mice (e.g., TRPC3 channel upregulation). A recent study in cerebral arteries suggested that intraluminal pressure-induced Ca^{2+} influx via TRPC6 channels enhances inositol triphosphate receptor (IP3R) activity. Ca^{2+} release through IP3Rs then activates nearby TRPM4 channels. The role of TRPM4 channels in initiating SMC membrane depolarization and vasoconstriction is well known (133). TRPC6 channels have also been shown to limit SMC proliferation via inhibition of phosphoinositide 3-kinase (PIP3)-protein kinase B (PKB) (Akt) pathway. Along similar lines, transforming growth factor (TGF-β) was shown to reduce TRPC6 channel activity, thereby enabling the Akt pathway and SMC proliferation (332). Convincing evidence in the literature supports the concept that TRPC6 channels enhance vascular tone. However, further research is needed to confirm the roles of TRPC6 channels in regulating blood pressure and SMC proliferation.

TRPM4 channel.: TRPM4 channels have emerged as an essential ion channel for pressure-induced depolarization of SMC membranes. TRPM4 channel is a Ca^{2+}-activated, Ca^{2+}-impermeable, non-selective cation channel (256). The unitary conductance of TRPM4 channel is approximately 24 pS. TRPM4 channel mostly conducts monovalent cations and shows minimal conductance for divalent cations (P_{Ca2+}/P_{Na+} = 0.09). Intracellular Ca^{2+}, via CaM binding, interacts with the C-terminal tail of TRPM4 channel and increases channel activity (EC_{50} = 300 nM) (241, 328). In SMCs, TRPM4 channel currents induce membrane depolarization and LTCC activation. TRPM4 channel knockdown with antisense oligonucleotides resulted in SMC membrane hyperpolarization and attenuated myogenic vasoconstriction (103). Moreover, PKC enhanced the Ca^{2+} sensitivity of TRPM4 channels, thereby facilitating myogenic vasoconstriction (102). Inhibition of IP3R Ca^{2+} release from the SR attenuated SMC TRPM4 channel activity, confirming the importance of IP3R Ca^{2+} signals for TRPM4 channel activity (132). A recent study showed that spatial coupling between TRPM4 and TRPC6 channels, brought about by their nanometer proximity,

facilitates myogenic constriction of cerebral arteries (133). Additionally, pressure-induced mechanical stretch resulted in PLCγ-dependent formation of inositol triphosphate (IP3). IP3, in turn, sensitized IP3Rs to TRPC6-mediated Ca^{2+} influx, thus creating microdomains of high Ca^{2+} that activated nearby TRPM4 channels (133). The physiological relevance of vascular TRPM4 channels was demonstrated in a study by Reading and Brayden (380). In this study, the authors showed that acute deletion of TRPM4 channels, accomplished by infusing antisense oligonucleotides into the cerebrospinal fluid, elevated cerebral blood flow. Moreover, myogenic vasoconstriction was reduced in cerebral arteries from the mice treated with TRPM4 antisense oligonucleotides (380). Surprisingly, $TRPM4^{-/-}$ mice are hypertensive, possibly due to increased catecholamine secretion (283). The discrepancies in the role of TRPM4 channels in controlling vasoconstriction and blood pressure could be resolved by using SMC-specific $TRPM4^{-/-}$ mice. Floxed TRPM4 mice have already been generated (217) and will prove useful in future investigations of SMC TRPM4 channels.

TRPP1/TRPP2 channels.: Ion channels of TRPP subfamily, TRPP1 and TRPP2 channels, have also been linked to the regulation of vascular function (Figure 3A). Stretch-activated cation channels (SACs) are thought to be key contributors to myogenic vasoconstriction (172, 394, 500). However, SACs remained poorly characterized. Studies by Sharif-Naeini showed that SMC-specific TRPP1 deletion decreased SAC currents in SMCs and attenuated myogenic vasoconstriction. Moreover, siRNA-induced TRPP2 knockdown in TRPP1-deficient arteries rescued SAC currents and myogenic vasoconstriction (411), suggesting an inhibitory effect of TRPP2 channels on SAC currents. In a recent study, mesenteric arteries from inducible, SMC-$TRPP1^{-/-}$ mice showed unaltered myogenic constriction but attenuated phenylephrine-evoked constriction (49). Moreover, SMC-$TRPP1^{-/-}$ mice had lower resting blood pressure. Additionally, SMC-$TRPP1^{-/-}$ mice were partially protected against Ang II-induced hypertension and vascular remodeling (49). The different effects of SMC-specific TRPP1 deletion on myogenic vasoconstriction in the two studies could be explained by inducible versus constitutive deletion of TRPP1 channels. Regardless, the SMC TRPP1 channel appears to be a vital controller of arterial contractility and could be a promising target for lowering the blood pressure in hypertension.

PIEZO1 channel.: PIEZO channels in vascular cells have been a topic of intense research in recent times. PIEZO proteins are mechanosensitive, non-selective cation channels that show a slight preference for Ca^{2+} over monovalent cations. Two PIEZO channel isoforms have been identified: PIEZO1 and PIEZO2 (75). Mammalian PIEZO1 channel shows a unitary conductance of approximately 30 pS, about 10 times higher than the Drosophila PIEZO1 channel (76). Mammalian PIEZO1 channel is a large protein composed of 2547 amino acids. Cryo-EM at 4.8 Å resolution revealed a trimeric three-bladed propeller-like structure of approximately 900 kDa for PIEZO1 channel. Each subunit has 14 TM α-helices. The channel pore is formed by two helices, outer (OH) and inner (IH) helix, located close to the C-terminal intracellular tail. The remaining 12 peripheral TM helices (PH) of each subunit contain the N-terminal tail, and function as mechanosensor units (127, 557). PIEZO1 channel is expressed at low levels in conduit arteries but is highly expressed in resistance arteries (93, 381). Although SMC-specific PIEZO1 deletion did not alter myogenic constriction of caudal and cerebral arteries, it was protective against SMC

remodeling in two different hypertension models. It was proposed that PIEZO1 channel induces the activation of Ca^{2+}-sensitive enzyme transglutaminase, which protects against SMC remodeling in hypertension (381). Studies of PIEZO1 channel in the vasculature are still in the early stages, and further research is needed to address the role of SMC PIEZO1 channels in vasoconstriction and blood pressure regulation.

Purinergic P2X receptor ion channels (P2XR).: Purinergic signaling is considered to be a crucial controller of vascular resistance and remodeling (Figure 3A). Endogenous purinergic receptor agonist, ATP, can be released by perivascular nerve terminals at the neuromuscular junctions (50) or by the opening of Pannexin-1 channels on SMC and EC membranes (35, 84, 205, 412). Amongst all known purinergic receptors, only P2X receptors (P2XRs) are ionotropic receptors. There are seven different P2XR subtypes (P2XR1-7) (330). Three subunits form functional P2XR. Each subunit is composed of intracellular N- and C-terminal tails linked to two α helix TM domains (TM1 and TM2, respectively), both connected to an extracellular ATP-binding domain (216). P2XRs are non-selective cation channels with similar permeability for monovalent and divalent cations and a single-channel conductance of 10 to 30 pS (398). ATP-P2XR signaling increased intracellular Ca^{2+} levels and contractility of SMCs from glomerular afferent arterioles, a response that was boosted by the AA metabolite 20-hydroxyeicosatetraenoic acid (20-HETE) (558). Moreover, inhibition of 20-HETE impaired ATP-induced constriction of glomerular afferent artery (559). Both P2X1R and P2X4R are expressed in arterial SMCs (149). Mesenteric arteries isolated from $P2X1^{-/-}$ mice showed impaired ATP- and nerve-induced-constriction (499).

Perivascular nerve stimulation causes spatially restricted Ca^{2+} influx signals through P2XRs in SMCs, described as junctional Ca^{2+} Transients (jCaTs) (Table 1). jCaTs can be easily distinguished from Ca^{2+} sparks from their wider spatial propagation (5 μm) and longer duration ($t_{1/2}$ = 145 ms) (239). Nerve stimulation-induced vasoconstriction has two components, an initial brief vasoconstriction mediated by jCaTs, followed by the α1AR-dependent prolonged vasoconstriction (238). jCaT-induced local membrane depolarization activates voltage-dependent Ca^{2+} channels (VDCCs) and stimulates Ca^{2+} release from the SR through IP3Rs (369). The role of P2X1R in mediating SMC contraction to ATP during sympathetic neurotransmission is well established. However, future studies are needed to address the functional roles of SMC P2X4Rs.

Na^+/Ca^{2+} exchanger (NCX).: NCX is another important regulator of SMC Ca^{2+} levels (Figure 3A). NCX is an antiporter system that moves Ca^{2+} in exchange for Na^+ across the plasma membrane (stoichiometric ratio $1Ca^{2+}$:$3Na^+$). The driving force and directionality of Na^+/Ca^{2+} exchange depend upon the chemical gradient of Na^+/Ca^{2+} ions across the plasma membrane and the membrane potential (41). Three different genes encode the three NCX isoforms (NCX1-3), amongst which NCX1 is the most abundant in SMCs (247). Crystal structure (1.9 Å resolution) revealed that NCX is a monomer composed of 10 TM helices (TM1-10). TM2-3 and TM7-8 form the core binding domains for Na^+/Ca^{2+} (254). Upon Na^+/Ca^{2+} binding, NCX undergoes a conformational change that alternatively exposes the ligand-binding domain to the extra- or intracellular compartment and allows Na^+/Ca^{2+} trafficking across the plasma membrane (171, 220, 326). Early studies suggested

that ATP increases the affinity of NCX to intracellular Ca^{2+} and extracellular Na^{+}. However, ATP was unable to influence NCX activity in the presence of saturating intracellular Ca^{2+} concentrations (42).

The first evidence of NCX in SMCs was reported in 1973 (382). Later studies suggested that NCX distribution on the plasma membrane is not random but is instead restricted to the regions underlying junctional SR (207). This localization pattern may suggest a role for NCX in regulating SR Ca^{2+} levels (40). Pharmacological inhibition (377) or SMC-specific deletion of NCX1 (509, 550) reduced cytosolic Ca^{2+} levels, impaired vasoconstriction, and lowered resting blood pressure. In a recent study by Zhang et al. (551), pressurized femoral arteries isolated from SMC-specific NCX1 overexpressing mouse (SM-NCX1-TG) showed increased SMC Ca^{2+} levels and higher myogenic constriction. SM-NCX1-TG mice also showed higher resting blood pressures. These findings support the idea that NCX1 mediates net Ca^{2+} influx into SMCs (known as a reverse mode) in resistance arteries. TRPM4 channels are known to mediate SMC depolarization by facilitating Na^{+} influx (133). Therefore, Na^{+} influx through TRPM4 channels may generate the driving force necessary for NCX to function in the reverse mode. However, further investigation is needed into the potential coupling of TRP channels with NCX protein.

NCX is modulated mainly by two intrinsic mechanisms. Na^{+}-dependent inactivation occurs when intracellular Na^{+} concentration reaches 100 nM (170). The other intrinsic modulation is by intracellular Ca^{2+}. By binding to a high affinity region on NCX, intracellular Ca^{2+} alleviates Na^{+}-dependent inactivation and augments NCX activity in both the forward and reverse modes. Regulatory Ca^{2+} does not get transported by NCX (249, 286). Li and colleagues (253) identified a specific region of 20 amino acids (XIP) on the intracellular N-tail of TM5 that showed a high binding affinity for Ca^{2+}-CaM. A synthetic exchanger inhibitory peptide (XIP) inhibited NCX activity by competing with the endogenous sequence. Single-site modifications of the XIP sequence drastically impaired Na^{+}-dependent inactivation and diminished Ca^{2+}-modulation of NCX (285). Additionally, high-affinity PIP2 biding to XIP eliminated the Na^{+}-dependent inactivation of NCX (165). In rabbit renal arterioles, PKC was also found to enhance NCX activity, although the precise site of action for PKC remains unclear (118).

Store-operated Ca^{2+} entry (SOCE) channels.: Several studies have focused on SOCE channels in SMCs; however, the functionality of SOCE in controlling vascular resistance remains controversial (98). SOCE is defined as Ca^{2+} influx activated by the depletion of ER/SR Ca^{2+} stores. The ionic currents recorded through SOCE are called Ca^{2+} release-activated Ca^{2+} current (CRAC). The two main proteins involved in mediating SOCE are stromal interaction molecule (STIM) and Orai. STIM is a single TM protein located on the ER membrane. The N-terminal tail contains the Ca^{2+}-sensitive domain (CSD) facing the ER lumen and comprises two sub-domains: EF-hand domain and sterile α-motif (SAM) domain. EF-domain is the Ca^{2+}-binding site that senses the decrease in ER Ca^{2+} levels. The C-terminal tail faces the cytosol and contains a 100-amino acid sequence called STIM-Orai activating region/CRAC activating domain (SOAR/CAD), which is pivotal for physical interaction with Orai. Orai is a 33 kDa protein located on the plasma membrane. It is a Ca^{2+}-selective pore formed by four TM segments and N- and C-terminal tails facing

the cytosol. Orai shows a very small unitary conductance (1 pS) and a high selectivity for Ca^{2+} (182). The depletion of ER Ca^{2+} leads to disassociation of Ca^{2+} from EF-hand domain, thereby promoting a conformational change that causes STIM monomer/dimers to oligomerize. CAD domain is required for store-dependent STIM oligomerization (78, 437). STIM oligomers tether with Orai channels through electrostatic interaction between SOAR/CAD and C-terminal tail of Orai channels. The STIM-Orai interaction creates the functional SOCE channel complex for replenishing the ER Ca^{2+} stores. It has also been suggested that STIM oligomers are tetramers with each monomer interacting with each of the four TM segments of Orai (78, 345). Two STIM (STIM1-2) and three Orai (Orai1-3) isoforms have been identified to date (87, 428).

The role of STIM and Orai in influencing SMC contractility is considered negligible. Indeed, Bisaillon and colleagues (36) reported that STIM and Orai expression is low in native SMCs. Orai- and STIM-deficient mice did not show impairment in vascular contractility (113). Studies over the past decade suggest that SOCE channels mostly control SMC proliferation and migration. Proliferative SMC culture showed higher Orai1 and STIM1 expression (368). In aortic SMC culture, knockdown of STIM1 and Orai1 impaired platelet-derived growth factor (PDGF)-induced migration. Furthermore, STIM1 and Orai1 were upregulated in SMCs from injured carotid arteries (36), and *in vivo* knockdown of STIM1 and Orai1 lowered neointima formation in injured carotid arteries (554). Overall, SOCE pathway in SMCs appears to be more important for SMC migration and proliferation than for the regulation of vascular contractility.

Ca^{2+} mobilization from intracellular organelles

Inositol trisphosphate receptors (IP3Rs)—The SR is an intracellular organelle characterized by high concentrations of both bound and free Ca^{2+} (100–700 μM) (410). A high concentration gradient for ER Ca^{2+} against cytosolic Ca^{2+} is created by Ca^{2+}-ATPase on the SR membrane (13, 299). Activation of IP3Rs on the SR membrane is one of the mechanisms for the release of SR Ca^{2+} into the cytosol (Table 1). Several mechanical and neurohumoral mediators, including pressure, Ang II, norepinephrine, endothelin-1, and serotonin, activate GqPCR-PLC signaling to increase IP3 formation and IP3R Ca^{2+} release. Out of the three IP3R isoforms (IP3R1-3) identified to date (117), IP3R1 and IP3R3 are expressed in arterial SMCs (Figure 3B) (312). IP3Rs are organized in micro-clusters of 2 μm diameter (277). Functional IP3R is a tetramer with each monomer consisting of six TM segments (TM1-6). N- and C-terminal tails face the cytosol and are linked to TM1 and TM6, respectively. The channel pore is lined by four TM6 segments (23). TM1-4 are located at the periphery and are connected to the pore unit TM5-6 by a lateral TM4-5 linker helix. Patch-clamp studies of the nuclear membrane reveal single-channel conductances of 113 pS at 0 mV and 300 pS at +60 mV for IP3Rs. IP3R is a bivalent cation-selective ion channel ($Ca^{2+}/K^{+} = 8$). IP3 relieves Ca^{2+}-inhibition of IP3R and enables Ca^{2+}-activation of the channel. The IP3-binding domain (IBC) is localized on the N-terminal tail of each subunit (117, 145, 541). Recent evidence suggests that the reversal of Ca^{2+}-inhibition of IP3R can occur when IP3 is bound to all four binding sites (14). However, prolonged exposure to IP3 (>2 s) causes IP3R to transition to an inactivated state that can only be recovered when IP3 is removed.

Ca^{2+} has a concentration-dependent, biphasic effect on IP3R activity. Ca^{2+} acts as pure agonist of IP3Rs at lower concentrations (0–300 nM Ca^{2+}) and turns into an inhibitor at higher concentrations (>300 nM Ca^{2+}) (190). Multiple Ca^{2+}-binding sites have been identified on different regions of IP3Rs (347, 422). The Ca^{2+}-regulation of IP3R activity is also dependent on IP3 levels. Increasing the concentration of IP3 reduces the affinity of Ca^{2+} for the inhibitory sites (278). Low levels of IP3 (10–30 nM) activate only one IP3R resulting in spatially restricted Ca^{2+} signals named “blips.” The amplitude of blips can reach approximately 30 nM above the baseline Ca^{2+} levels. Progressively higher IP3 concentrations (30–60 nM) recruit more IP3Rs within the same cluster, resulting in a larger Ca^{2+} release that potentiates the signal via Ca^{2+}-induced Ca^{2+}-release. These larger IP3R-mediated Ca^{2+} events are called “puffs.” The occurrence of puffs requires activation of approximately five IP3Rs in a cluster, and puff amplitude was recorded to be 170 nM above the basal Ca^{2+} levels. Modeling studies of IP3R kinetics and spatial spread of Ca^{2+} indicate that cooperative activation of two IP3Rs can occur with high probability only if they are approximately 12 nm apart. Increasing the distance up to 50 nm reduced the cooperative activation to 50% (449, 454, 539). Even higher IP3 levels relieve Ca^{2+}-dependent IP3R inhibition and facilitate Ca^{2+} release from multiple IP3R clusters, triggering the formation of Ca^{2+} waves that can propagate across the cell. While Ca^{2+} puffs are terminated by Ca^{2+} binding to the inhibitory sites on IP3Rs, Ca^{2+} waves seem to dissipate upon IP3-unbinding from IP3R (391).

In cremaster arteries, IP3R inhibition impaired Ca^{2+} waves and myogenic vasoconstriction (516). However, IP3R1 knockdown did not alter myogenic vasoconstriction in mesenteric arteries (556), suggesting heterogeneity in the role of IP3Rs among different vascular beds. In a recent study, Gabani and colleagues (122) showed that the small noncoding RNA (MiR-204) lowers IP3R1 expression in mesenteric arteries. MiR-$204^{-/-}$ mice showed higher expression of IP3R1, increased Ang II-induced vasoconstriction, and a higher increase in blood pressure in response to Ang II. Inhibition of IP3R also impaired SMC proliferation in cerebral arteries (518). Thus, IP3R Ca^{2+} signaling plays a pivotal role in regulating SMC contractility and proliferation.

Ryanodine receptors (RyRs)—RyR is a Ca^{2+}-permeable ion channel located on the SR membrane. Recent high-resolution Cryo-EM (4.8 Å) studies show that the functional channel comprises four subunits, 560 kDa each. Each subunit has six TM helices. The pore is formed by TM5-6 and segment P, which acts as a selectivity filter. Under physiological conditions, segment P and TM6 have many negatively charged amino acid residues, thereby facilitating high unitary conductance of 103 pS (338, 545). The N-terminal tail linked to TM1 is a large structure (2217 amino acids) facing the cytosol. It encompasses different binding sites essential for RyR channel regulation, including the CaM-like domain (EF-hands) that constitutes the conserved Ca^{2+}-binding domain (CBD) (529). RyR is activated upon Ca^{2+} binding to EF-hands (33, 545). Three RyR isoforms have been identified-RyR1-3 (467, 564), and all three have been shown to be expressed in SMCs (321).

Ca^{2+} release from RyRs in SMCs was, for the first time, described in cerebral arteries (318). The individual Ca^{2+} release signals through RyRs were termed “Ca^{2+} sparks” (Table 1), akin to the previously described Ca^{2+} sparks in cardiac myocytes (66). Ca^{2+} sparks

peak in approximately 20 ms, decay in approximately 200 ms, and are mediated by the activation of four to six RyRs. They produce highly localized increases in Ca^{2+} (10–100 μM) within 20 nm diameter from the site of initiation (67, 203). RyRs can be activated by Ca^{2+} influx from the extracellular environment or Ca^{2+} release from nearby IP3Rs or RyRs. SMC membrane potential is a well-known regulator of RyR activity. Membrane depolarization-induced increase in the activity of Ca^{2+} sparks was linked to Ca^{2+} entry via LTCCs (226) and TTCCs (150). Notably, membrane depolarization, *per se,* did not activate Ca^{2+} sparks when extracellular Ca^{2+} was replaced with Ba^{2+} as a charge carrier (420). Jaggar et al. (204) reported that SMC membrane depolarization from −70 to −30 mV increases Ca^{2+} spark activity. Moreover, $Ca_V3.2$ channels were essential for triggering Ca^{2+} sparks under physiological membrane potentials (−40 mV), whereas $Ca_V1.2$ channels were the predominant source of Ca^{2+} for Ca^{2+} spark activity at depolarized membrane potentials (−20 mV). Interestingly, NCX, activated in the reverse mode, was found to be partially responsible for Ca^{2+} spark initiation at −20 mV (162).

SMC RyRs are a crucial negative regulatory mechanism for myogenic vasoconstriction. Myogenic vasoconstriction involves pressure-induced SMC membrane depolarization followed by VDCC activation. Ca^{2+} influx through VDCCs activates RyR Ca^{2+} sparks, which stimulate the activity of nearby BK channels, causing membrane hyperpolarization and vasodilation (226, 318). In partially depolarized SMCs (Em = −40 mV), most Ca^{2+} sparks are associated with spontaneous transient outward current (STOC) that represent activation of roughly 18 BK channels. The probability of STOCs increases to 10^4 when associated with Ca^{2+} sparks, suggesting a strong spatial interaction between RyRs and BK channels. Since BK channels exhibit a low Ca^{2+} affinity (100–200 μM), their activation requires high levels of Ca^{2+}. Spatial coupling between RyRs and BK channels ensures high local Ca^{2+} concentrations (10–100 μM) near (~20 nm) the Ca^{2+} spark foci (353, 537). Intracellular microtubule structures are essential for ensuring spatial proximity between RyRs and BK channels. Indeed, disruption of microtubules uncoupled RyRs from BK channels and increased myogenic vasoconstriction in cerebral arteries (373). While SMC RyRs are known for their vasodilatory role, Krishnamoorthy et al. (233) demonstrated that a high-level activation of RyRs could contribute to whole-cell increases in Ca^{2+} and vasoconstriction in response to nerve stimulation.

Studies on the role of individual RyR isoforms in SMCs have been challenging as $RyR1^{-/-}$ (465) and $RyR2^{-/-}$ (466) mice are lethal. Lohn et al. (266) addressed the role of RyR3 in Ca^{2+} spark singling. Interestingly, $RyR3^{-/-}$ mice showed increased Ca^{2+} spark frequency and reduced myogenic vasoconstriction. These findings suggest that RyR3 may negatively regulate RyR1 and RyR2 activity. In a recent study, Kassmann and colleagues (215) reported higher myogenic vasoconstriction and elevated blood pressure in SMC-specific, tamoxifen-inducible $RyR2^{-/-}$ mice. The generation of SMC-specific $RyR2^{-/-}$ may be the necessary first step in understanding the relative contribution of specific RyR isoforms to Ca^{2+} spark activity in SMCs and their role in blood pressure regulation.

Ca^{2+}-ATPase (SERCA)—Cytosolic Ca^{2+} levels in SMCs are lowered mainly by Ca^{2+} uptake into the SR via the SERCA on the SR membrane (Figure 3B). SERCA is encoded by three different genes, SERCA1-3 (355), and different splice variants of these genes have

been documented. In SMCs, the predominant isoform is SERCA2b, followed by SERCA2a and SERCA3 (523). SERCA is a P-type ATPase that was discovered by Nobel laureate Jens Skou in the year 1957. A common feature of P-type pumps is to undergo two main conformational changes (E1 and E2), with the formation of a phosphorylated (P) aspartyl intermediate (E1-E2), which gives the family its name. E1 state has a high affinity for Ca^{2+}, and E2 state has a low affinity for Ca^{2+} (376). The transition from E1 to E2 is ATP-dependent (Figure 4). In each cycle, SERCA uses one molecule of ATP to pump two Ca^{2+} into the SR in exchange for two to three H^+ released into the cytosol (523).

X-ray crystallography studies showed that SERCA comprises three cytoplasmic domains (A, N, and P) and a TM domain. The TM domain is characterized by 10 TM helices (TM1-10). TM4 and TM5 are longer and protrude from the SR membrane to the cytosol. Two putative Ca^{2+}-binding sites have been identified on the TM domains-site I between TM5 and TM6, and site II on TM4. The N (nucleotide) domain is essential for ATP binding, and ATP-dependent phosphorylation of domain P. Asp^{351} found in domain P is highly conserved across species and is pivotal for the formation of high energy phosphorylated-aspartyl intermediate. The A domain transduces the conformational change of domain P to TM domain (337, 487) (Figure 4). At low cytosolic Ca^{2+} concentrations, SERCA is inhibited by phospholamban. Phospholamban is a 52-amino acids membrane integral protein that binds to the low Ca^{2+} affinity E2 state and inhibits the activity of the pump. Inhibition is relieved either by an increase in cytosolic Ca^{2+} or by phosphorylation of phospholamban by PKA (513) or Ca^{2+}-CaMKII (275).

Wellman and colleagues (513) reported higher Ca^{2+} spark and STOC frequency in arteries from phospholamban$^{-/-}$ mice due to increased SR Ca^{2+} loading. These findings implied that SERCA might influence IP3R and RyR Ca^{2+} signaling by altering SR Ca^{2+} loading. Schneider and colleagues (404) showed that phospholamban phosphorylation by 5′-AMP-activated protein kinase (AMPK) disinhibits SERCA, promotes Ca^{2+} sequestration into the SR, and causes vasodilation. Moreover, the elevation of extracellular K^+ from 3 to 6mM dilated cerebral arteries, an effect that was prevented by SERCA inhibition (179, 288). SERCA is also known to be a potent inhibitor of SMC proliferation (518). SERCA2a was shown to impair injury-induced SMC proliferation via inhibition of calcineurin-nuclear factor of activated T-cells (NFAT) signaling (259). SERCA2 deletion is embryonic lethal (356); therefore, generating SMC-specific SERCA2$^{-/-}$ mice may be desirable for obtaining precise insights into the physiological roles of SMC SERCA2.

TRPML1 channel—Ion channels of the TRPML subfamily (TRPML1-3) are encoded by Mcoln1, Mcoln2, and Mcoln3 genes. TRPML channels are mainly localized in the membranes of late endosomes (LEL) (68). Thakore and colleagues (474) recently demonstrated the importance of TRPML1 channels in regulating SMC contractility and blood pressure (Figure 3B). Endosomal TRPML1 channels colocalized with RyR2 channels. Ca^{2+} release from LEL through TRPML1 channels activated RyRs and lowered vascular resistance. Moreover, TRPML1-deficient (Mcoln1$^{-/-}$) mice showed elevated blood pressure and increased vasoconstriction. Thus, SMC TRPML1 channels appear to be important regulators of vascular resistance and blood pressure.

Endothelial Cell Ca^{2+} Signals in Small Arteries and Arterioles

The endothelium is a single cell layer of cells that lines the inner walls of all the blood vessels. ECs are constantly exposed to the mediators in the blood and mechanical forces exerted by the bloodstream. Endothelial function in arteries and arterioles is also modulated by stimuli from SMCs (126, 178, 313, 488). In this section, we will focus on the physiological Ca^{2+} signaling mechanisms that alter EC function. ECs in resistance-sized arteries send out projections, across the internal elastic lamina, to the SMC layer. The sites of contact between ECs and SMCs are enriched with connexin proteins (Cx37, Cx40, and Cx43) that form myoendothelial gap junctions (MEGJs) (143, 196, 400). MEGJs are characterized by two hemichannels, one each on the EC and SMC membranes. Each hemichannel is a hexamer composed of six connexins (32). MEGJs allow the passage of second messengers and electrical signals (92, 104, 178, 284), and serve as a crucial communication site for ECs and SMCs. ECs can influence the contractile state of the adjacent SMCs via endothelium-derived hyperpolarization (EDH) or by releasing substances that activate vasodilatory signaling in SMCs in a paracrine manner. The preferential activation of one pathway over another may be determined by the vascular bed under consideration (341) and the size of the artery (419, 492). Recent studies show that neighboring ECs are heterogeneous with respect to Ca^{2+} signaling mechanisms (246). Indeed, McCarron and colleagues demonstrated that neighboring ECs are organized into Ca^{2+} signaling clusters, and communication amongst these clusters is essential for normal vascular function (246). Here, we elaborate on the Ca^{2+} signaling pathways that initiate EC to SMC, SMC to EC, and EC to EC communications in the vascular wall, and the target proteins that transduce the Ca^{2+} signals into a physiological response.

Ca^{2+} influx from extracellular compartment

Non-voltage-gated Ca^{2+} entry pathways (TRP channels, PIEZO channel, P2X receptor, SoCE channels, and Na^+/Ca^{2+} exchanger)

TRPA1 channel.: In the past decade, TRPA1 channels have emerged as a crucial Ca^{2+} influx pathway in ECs from specialized vascular beds. TRPA1 channels show a unitary conductance of approximately 96 pS at −60 mV (309), and a higher permeability to Ca^{2+} than Na^+ (P_{Ca2+}/P_{Na+} = 7.9) (213). TRPA1 channels are activated by several pungent natural compounds in food such as allicin (garlic) (276), allyl isothiocyanate (mustard), and cinnamon (cinnamaldehyde) (200). TRPA1 channels are gated by extracellular Ca^{2+} in a voltage-dependent manner. In patch-clamp studies, TRPA1 channels displayed slow activation at a holding potential of −80 mV and in the absence of extracellular Ca^{2+}. However, in the presence of extracellular Ca^{2+} and ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid (EGTA)-buffered intracellular Ca^{2+}, holding potential of −80 mV caused fast channel activation followed by fast inactivation. Notably, fast channel inactivation did not occur at a more depolarized membrane potential (−20 mV) (309).

Earley and colleagues (99) provided the first evidence for vasodilatory effects of endothelial TRPA1 channel activation in cerebral arteries. TRPA1 channels co-localized with intermediate-conductance Ca^{2+}-activated K^+ (IK) channels at MEPs (Figure 5). Ca^{2+} influx through TRPA1 channels (Table 1) activated nearby IK channels, resulting in EC

membrane hyperpolarization and vasodilation. Moreover, the vasodilatory effect of TRPA1-IK channels was boosted by inward-rectifier potassium (K_{ir}) channels on SMC membranes. In a subsequent study, TRPA1 channels were shown to promote IP3R Ca^{2+} release from the ER. Furthermore, endothelial TRPA1 channel activation inhibited the formation of Ca^{2+} waves in SMCs, providing additional evidence supporting the inhibitory effect of endothelial TRPA1 channels on SMC contraction (375).

ROS and products formed by lipid peroxidation, including 4-hydroxynonenal (4-HNE), are the main endogenous modulators of endothelial TRPA1 channel activity (97, 490). ROS generating enzyme NADPH oxidase 2 (NOX2) was present in nanometer proximity with TRPA1 channel in cerebral arteries. NOX2-generated ROS induced membrane lipid peroxidation and 4-HNE formation, thereby increasing TRPA1 channel activity and causing vasodilation. This effect was blunted in the arteries from endothelium-specific $TRPA1^{-/-}$ mice (448). Studies by Pires and colleagues (359) suggested that endothelial TRPA1 channels are neuroprotective under hypoxic conditions. Under hypoxic conditions, mitochondrial ROS production enhanced TRPA1 channel-mediated dilation of cerebral arteries. In support of this concept, endothelium-specific $TRPA1^{-/-}$ mice showed larger cerebral damage following stroke-induced hypoxia. Overall, the current evidence suggests a central role for endothelial TRPA1 channels in mediating Ca^{2+} influx in the cerebral vasculature.

TRPV4 channel.: TRPV4 is one of the most studied Ca^{2+} influx pathways in the intact endothelium. Until recently, the physiological roles of endothelial TRPV4 channels were not known (reviewed in Ref. 63). Systemic administration of a potent and selective TRPV4 channel agonist evoked a dose-dependent drop in blood pressure in dogs, rats, and mice (519). Moreover, acetylcholine-induced decrease in blood pressure was attenuated in global $TRPV4^{-/-}$ mice (549). However, global $TRPV4^{-/-}$ mice showed unaltered resting blood pressure (178, 549), possibly due to a compensatory upregulation of other ion channels or the absence of TRPV4 channels from multiple cell types in these mice. Ottolini and colleagues (342), in a recent study, demonstrated the importance of endothelial TRPV4 channels and its regulation by AKAP150 in lowering the resting blood pressure. In this study, tamoxifen-inducible, endothelium-specific $TRPV4^{-/-}$ or $AKAP150^{-/-}$ mice showed higher resting blood pressures, confirming the pivotal role of endothelial AKAP150-TRPV4 signaling in blood pressure regulation.

Multimodal physiological stimuli can activate endothelial TRPV4 channels. Early studies supported a mechanosensory role of endothelial TRPV4 channels, although recent evidence suggests that TRPV4 channels are not direct mechanosensors (327). An alternative explanation for mechanoactivation of TRPV4 channels is that the channels can be activated by mechanical stimuli via signaling pathways involving the activation of cytochrome P450 (CYP) epoxygenases and EET production (101, 268). Kohler and colleagues (228) demonstrated that sheer stress-induced vasodilation in rat gracilis arteries is reduced by ruthenium red (RuR), a non-selective TRPV4 channel blocker. Flow-induced, TRPV4 channel-mediated vasodilation was also reported in carotid arteries (158) and mesenteric arteries (291) (Figure 8). Inhibiting AA metabolism eliminated sheer stress-induced vasodilation, suggesting that AA metabolites are necessary for mechanotransduction by

TRPV4 channels. In cremaster arteries, sheer stress increased the functional coupling of M3 muscarinic receptors with endothelial TRPV4 channels for vasodilation (82). Bagher and colleagues (20) showed that low intravascular pressure (5–50 mmHg) enhances the activity of endothelial TRPV4 channels, further supporting the activation of endothelial TRPV4 channels by mechanical stimuli. Studies by Saliez et al. (396) in EC culture demonstrated that TRPV4 channels co-immunoprecipitate with caveolin-1. Moreover, endothelial Ca^{2+} influx was impaired in the absence of caveolin-1. Although a direct interaction between caveolin-1 and TRPV4 channel appears likely, the functional evidence on caveolin-1 regulation of TRPV4 channel activity is lacking. Studies using EC-specific caveolin-1 knockout mice will be crucial for unraveling the functional and physiological significance of caveolin-1-TRPV4 channel interaction in the endothelium.

Multiple endogenous modulators of endothelial TRPV4 channels have been identified. TRPV4 channel activity is heavily influenced by GqPCR-PLC signaling in both arterial and capillary endothelium (153, 432, 433). PLC-DAG-activated PKC can phosphorylate TRPV4 channels and potentiate their activity (111). Moreover, PLC-mediated decrease in PIP2, a negative modulator of TRPV4 channels, increases TRPV4 channel activity (153, 461). Furthermore, IP3 was shown to bind to TRPV4 channels and increase their activity (178, 461). As described with SMC TRPV4 channels, Ca^{2+} itself has a biphasic effect on TRPV4 channel activity. In ECs, Ca^{2+} influx through TRPV4 channels potentiated the activity of the neighboring TRPV4 channels in a cluster, resulting in cooperative channel openings (432, 433). On the contrary, NO impaired the cooperative openings of TRPV4 channels via activation of endothelial guanylyl cyclase (GC)-PKG pathway (282, 540) and reduced channel activity. Hong and colleagues (178) described the presence of a myoendothelial feedback mechanism whereby α1AR stimulation-induced vasoconstriction was limited by endothelial TRPV4 channels (Figure 6). Phenylephrine (PE) activated SMC α1ARs and increased the levels of IP3, which diffused across the MEGJs to ECs and activated TRPV4 channels at MEPs. H_2S, a gasotransmitter molecule produced by ECs, was shown to activate endothelial TRPV4 channels in a study by Naik and colleagues (310). H_2S-activation of TRPV4 channels increased endothelial BK channel currents. The authors also showed that H_2S induces sulfhydration of endothelial TRPV4 channels. Further studies to identify the precise site of action for H_2S on the TRPV4 channel are awaited.

The detrimental effects of excessive TRPV4 channel activity in pulmonary endothelium are well known (12, 451, 478, 540), although the physiological roles of pulmonary endothelial TRPV4 channels have not been resolved. Marziano et al. (282) showed that ATP activates endothelial TRPV4 channels via P2 purinergic receptor signaling in resistance pulmonary arteries. However, global $TRPV4^{-/-}$ mice showed unaltered mean pulmonary arterial pressure (PAP) (528). In this regard, TRPV4 channels are also expressed in SMCs from pulmonary arteries (281), where they promote vasoconstriction (430). Therefore, lack of a PAP phenotype in $TRPV4^{-/-}$ mice could be due to the activation of compensatory mechanisms in SMCs and ECs. Future studies in EC-specific $TRPV4^{-/-}$ (342) and SMC-specific $TRPV4^{-/-}$ are warranted to separate the contributions of endothelial and SMC TRPV4 channels to the regulation of PAP.

Unitary Ca^{2+} influx signals through TRPV4 channels, called TRPV4 Ca^{2+} sparklets (Table 1), have been recorded in the intact endothelium from resistance arteries and in EC culture (432, 447). Notably, TRPV4 sparklets are not randomly distributed throughout the EC membrane. Instead, the majority of TRPV4 sparklet activity was observed at MEPs (Figure 5) (178, 432, 433). It was later proposed that MEP-localized AKAP150 anchors PKC in the vicinity of TRPV4 channels and facilitates the coupling among TRPV4 channels (433). IK and SK channels also localize to MEPs (20, 244, 400), explaining the preferential activation of IK/SK channels by TRPV4 sparklets in systemic resistance arteries (341). Contrary to the systemic arteries, TRPV4 sparklets selectively activated endothelial nitric oxide synthase (eNOS) to dilate resistance pulmonary arteries (282). Very recently, Ottolini et al. (341) provided evidence that spatial coupling determines the TRPV4 sparklets-target linkage in different vascular beds (Figure 7). In this study, the authors showed that TRPV4 channels co-localize with IK/SK channels at MEPs in resistance mesenteric arteries. MEPs in this vascular bed are also enriched with hemoglobin α (Hbα) (440), a protein that limits NO release and diffusion (440). TRPV4 channels also localize at MEPs in resistance pulmonary arteries. However, Hbα is absent from MEPs in resistance pulmonary arteries. Additionally, IK/SK channels do not localize at MEPs in this vascular bed. These differences in spatial coupling favor TRPV4-IK/SK channel signaling in resistance mesenteric arteries and TRPV4-eNOS signaling in resistance pulmonary arteries.

TRPV3 channel.: Consistent with other ion channels of TRPV subfamily, TRPV3 channels show high unitary conductance (~170 pS at +60 mV) and Ca^{2+} permeability (P_{Ca2+}/P_{Na+} = 12). An increase in temperature from 25 to 37 °C increases the outward currents through TRPV3 channels nearly fourfold (531). TRPV3 channels are also activated by dietary monoterpenes, including carvacrol, thymol, vanillin, and ethyl-vanillin (530). Earley and colleagues (100) provided the first evidence for the functional expression of TRPV3 channels in ECs from cerebral arteries (Figure 5). Endothelial TRPV3 channel activation by carvacrol dilated cerebral arteries through IK/SK channels. In a more recent study, Pires et al. (360) recorded unitary Ca^{2+} influx events through TRPV3 channels (TRPV3 sparklets, Table 1) in ECs from cerebral parenchymal arterioles. The authors reported that TRPV3 sparklets show higher single-channel amplitudes when compared to TRPA1 sparklets, results that are consistent with a higher unitary conductance of TRPV3 channels. Endothelium-specific knockout for TRPV3 channels has not been generated; therefore, the physiological roles of endothelial TRPV3 channels remain unclear.

TRPV1 channel.: The expression and function of TRPV1 channels in ECs are controversial. Several studies have relied upon TRPV1 channel antibodies to assess its endothelial expression, although the specificity of these antibodies has not been verified using knockout tissue (484). In two recent studies on transgenic TRPV1-LacZ and TRPV1-Cre:tdTomato mice, TRPV1 channels were expressed in the SMC layer but not in the endothelial layer (57). Nevertheless, some studies have proposed an important role for TRPV1 channels in endothelium-dependent vasodilation. Yang and colleagues (535) suggested that TRPV1 channel agonist capsaicin activated eNOS and dilated mesenteric arteries, effects that were absent in the arteries from $TRPV1^{-/-}$ mice. TRPV1-eNOS signaling in the vasculature has also been proposed by other studies (46, 483). It

should be noted that capsaicin can activate TRPV1 channels in sensory nerves to release calcitonin gene-related peptide (CGRP) and substance P (SP) (279), which could affect the endothelium. Therefore, a definitive assessment of the role of endothelial TRPV1 channels in vasodilation awaits the development of endothelium-specific TRPV1$^{-/-}$ mice.

TRPC channel.: Multiple studies have reported significant roles for endothelial TRPC channels as Ca^{2+} influx pathways in resistance arteries. TRPC1 channels formed heteromeric complexes with TRPV4 channels in freshly dissociated ECs from rabbit mesenteric arteries. Furthermore, TRPC1-TRPV4 complex activated eNOS and caused vasodilation (138). Ma and colleagues (273) indicated that the TRPC1-TRPV4 channel complex plays a crucial role in sheer stress-induced increase in endothelial Ca^{2+} and vasodilation. In a study by Senadheera and colleagues (409), TRPC3 channels were found to be localized with IK/SK channels at MEPs of rat mesenteric arteries (Figure 5). Moreover, TRPC3-IK/SK channel signaling mediated acetylcholine-induced dilation in these arteries (409). Co-localization of TRPC3 channels with SK/IK channels at MEPs was also observed in rat popliteal arteries. Additionally, rat mesenteric arteries treated with TRPC3 antisense oligonucleotides showed impaired relaxation to bradykinin (261), further supporting a role for TRPC3 channels in endothelium-dependent vasodilation. In a recent study, ATP-induced EC hyperpolarization was shown to have two components: an early hyperpolarization through IK channels; and a sustained hyperpolarization through TRPC3-SK channel signaling, revealing a central role for TRPC3 channels in ATP-induced endothelial hyperpolarization (227).

TRPM2 channel.: The unitary conductances of TRPM2 channel are 58 and 76 pS at negative and positive voltages, respectively. TRPM2 channel is equally permeable to divalent and monovalent cations (401). The activity of TRPM2 channels was shown to be increased by H_2O_2, an important redox signaling molecule with a vasodilatory activity (232, 270). A recent study in cremaster arteries showed that H_2O_2-induced vasodilation is impaired by an antibody against TRPM2 channels, and by inhibiting SK/IK channels (70). Therefore, endothelial TRPM2-SK/IK signaling may underlie H_2O_2-dependent vasodilation, although further studies are required to confirm the role of TRPM2 channels in controlling endothelial function.

TRPP1 channel.: TRPP1 channel is encoded by PKD2, a gene mutated in patients with autosomal-dominant polycystic kidney disease (296). The outward unitary conductances of TRPP1 channel for Ca^{2+}, Na^+, and K^+ are 90, 99, and 117 pS, and inward conductances are 4, 89, and 144 pS, respectively. TRPP1 channels conduct ionic currents with permeability ratios of P_{K+}: P_{Na+}:P_{Ca2+} of 1:0.4:0.025 (264). In a recent study, MacKay and colleagues (274) demonstrated the importance of endothelial TRPP1 channel in mediating flow-induced dilation of mesenteric arteries (Figure 8). Pressurized mesenteric arteries from endothelium specific TRPP1$^{-/-}$ mice showed impaired dilation to shear stress. Moreover, endothelium-specific TRPP1$^{-/-}$ mice had higher diastolic and systolic blood pressures. Thus, endothelial TRPP1 channels appear to be a key element in EC mechanosensing and vasodilation.

Purinergic P2X receptor ion channels (P2XR).: Evidence in the literature supports a functional role for P2X1, P2X3, and P2X4 purinergic receptors in ECs. P2X1 receptor was found to be expressed on the endothelium of mesenteric arteries from rats (157) and mice (156) (Figure 8). Endogenous purinergic receptor agonist ATP induced a dilation of mesenteric arteries; an effect that was blunted by inhibition of SK/IK channels (157). Importantly, ATP failed to dilate mesenteric arteries from $P2X1^{-/-}$ mice, supporting the idea that ATP activates P2X1 receptors in this vascular bed (156). Immunohistochemistry analysis by Glass and colleagues (130) showed that P2X3 receptor is expressed in the endothelium from thymus arteries. Moreover, Yamamoto et al. (534) found that ATP- and flow-induced vasodilation is markedly reduced in cremaster and mesenteric arteries from $P2X4^{-/-}$ mice. Furthermore, $P2X4^{-/-}$ mice had a hypertensive phenotype accompanied by a reduction in nitrite and nitrate production. These results led the authors to postulate that impaired eNOS activity and NO production may be partially responsible for increasing blood pressure in the $P2X4^{-/-}$ mice.

PIEZO1 channel.: Endothelium-dependent vasodilation in response to blood flow/shear stress is well established; however, the exact endothelial mechanosensor underlying this effect has remained elusive. PIEZO1 channel on EC membrane has recently emerged as the mechanosensor for flow/shear stress-induced changes in vascular resistance (Figure 8). Wang and colleagues (506) showed that PIEZO1 channels mediate the dilation to flow/shear stress via eNOS activation in U46619 pre-constricted third- and fourth-order mesenteric arteries. Mesenteric arteries from endothelial $PIEZO1^{-/-}$ mice (EC-$PIEZO1^{-/-}$) showed impaired flow-induced vasodilation. Furthermore, PIEZO1 channel promoted extracellular ATP release via Pannexin1/2 channels in response to flow. ATP, in turn, activated eNOS via P2Y2 purinergic receptor signaling. Consistent with impaired vasodilation, EC-$PIEZO1^{-/-}$ mice showed higher resting systolic blood pressures (506). On the contrary, Rode and colleagues reported that endothelial PIEZO1 channels cause flow-induced vasoconstriction of second-order mesenteric arteries during whole-body exercise. EC-$PIEZO1^{-/-}$ mice on a running wheel showed lower systolic and diastolic blood pressures. Moreover, endothelial PIEZO1 deletion did not affect the reactivity of larger arteries (saphenous and carotid arteries). The discrepancy in results between the two studies could be explained by blood pressure recordings during exercise versus resting conditions, and studies of vascular function using pressure myography versus wire myography. In a recent study, Lhomme and colleagues (250) demonstrated the importance of endothelial PIEZO1 channels in triggering relaxation of pulmonary arteries via NO production. Furthermore, endothelial PIEZO1 channel-induced vasorelaxation was not impaired in a mouse model of pulmonary hypertension. Thus, regardless of the conflicting reports, strong evidence supports the functional significance of endothelial PIEZO1 channels.

Na^+/Ca^{2+} exchanger (NCX).: A recent study demonstrated that NCX contributes to acetylcholine-induced dilation of mesenteric resistance arteries (255). Lillo et al. (255) showed that during acetylcholine activation of endothelial muscarinic receptor signaling, NCX works in reverse mode (NCXrm), enhancing Ca^{2+} entry in the endothelium and facilitating endothelium-dependent vasodilation. Moreover, NCX was concentrated within the caveolae, in nanometer proximity to eNOS. This result may suggest NCXrm-eNOS

signaling during acetylcholine-induced vasodilation. Most other studies have used cell culture systems or conduit arteries (129, 136, 405). Overall, the involvement of NXC in influencing endothelial Ca^{2+} signaling in resistance arteries and arterioles remains poorly understood.

Ca^{2+} release from intracellular compartments

Inositol trisphosphate receptors (IP3Rs)—All three isoforms of IP3Rs (IP3R1-3) have been reported in ECs. Ledoux and colleagues (244) described spatially restricted IP3R Ca^{2+} release from the ER at MEPs. These events were termed "Ca^{2+} pulsars" (Table 1). The kinetic properties of Ca^{2+} pulsars allow a clear distinction between Ca^{2+} puffs and Ca^{2+} waves. When compared to Ca^{2+} sparks, Ca^{2+} pulsars showed slower rise times and longer durations. Consistent with the occurrence of Ca^{2+} pulsars at MEPs, IP3Rs were also shown to localize at MEPs. Ca^{2+} pulsars signaled through IK channels to induce EC hyperpolarization and vasodilation (Figure 5). In a recent study, conditional endothelial IP3R1 deletion did not alter vascular dynamics. However, endothelium-specific triple $IP3R^{-/-}$ mice (ECTKO) resulted in higher resting blood pressures. Second-order mesenteric arteries from ECTKO mice also showed impaired acetylcholine-induced dilation (257).

As described for SMCs, EC IP3R activity is also influenced by Ca^{2+} influx pathways. Heathcote and colleagues (166) explained that Ca^{2+} influx through endothelial TRPV4 channels triggers IP3R opening. Ca^{2+} release via IP3Rs amplifies the initial increase in Ca^{2+} through TRPV4 channel activation, resulting in long and sustained Ca^{2+} waves that lower vascular contractility. The focal application of acetylcholine on cremasteric arteries resulted in the formation of Ca^{2+} waves that propagated for over 1 mm with a velocity of 116 μm/s. Interestingly, the initial vasodilatory responses to acetylcholine preceded the propagation of Ca^{2+} waves. The authors described two temporally distinct vasodilatory phases—an early "electrically conducted vasodilation" occurring through the transmission of hyperpolarizing signal and a later "Ca^{2+} wave-dependent vasodilation"(21, 468). Communication through gap junctions was found to be pivotal for the propagation of Ca^{2+} waves between neighboring ECs (105).

IP3 and Ca^{2+} play crucial roles in the myoendothelial feedback mechanism that limits α1AR-induced SMC contraction (Figure 6). Garland and colleagues recently demonstrated phenylephrine-induced increase in SMC Ca^{2+} and diffusion of SMC Ca^{2+} to MEPs via MEGJs, giving rise to the signals called VECTors (VDCC-dependent Endothelial cell Ca^{2+} Transients). VECTors activated endothelial IP3Rs and facilitated the formation of Ca^{2+} puffs and Ca^{2+} waves in the endothelium. In summary, the study by Garland and colleagues (126) suggested that the diffusion of Ca^{2+} from SMCs to ECs across MEGJ can counteract α1AR-induced vasoconstriction. In another study, endothelial TRPV4 sparklets were implicated as an essential element of the myoendothelial feedback mechanism. Phenylephrine-induced vasoconstriction was counterbalanced by the diffusion of IP3 from SMCs to ECs across MEGJs and subsequent activation of TRPV4 channels at MEPs. Interestingly, the authors observed that endothelial TRPV4 channel activity is influenced only by diffusion of IP3 and not Ca^{2+} from SMCs to ECs (178). Tran and colleagues (488) provided further evidence for IP3 diffusion from SMCs to ECs during phenylephrine-induced vasoconstriction. α1AR

signaling resulted in IP3R activation at MEPs and formation of distinct Ca^{2+} events termed "Ca^{2+} wavelets" (Table 1). Ca^{2+} wavelets could be distinguished from Ca^{2+} puffs based on their longer duration and larger spatial spread. Ca^{2+} wavelets activated nearby IK/SK channels at MEPs to limit α1AR-induced vasoconstriction. Similarly, Nausch et al. (313) suggested that sympathetic nerve stimulation activates IP3R Ca^{2+} pulsars at MEPs and limits sympathetic vasoconstriction. Finally, the Ca^{2+}-binding chaperon protein calreticulin (Calr) was also shown to play an important role in myoendothelial feedback mechanism. Calr was highly localized at MEPs in mesenteric arteries. α1AR-induced increase in endothelial Ca^{2+} signals at MEPs was absent in the arteries from endothelial $Calr^{-/-}$ mice, which resulted in higher α1AR-induced vasoconstriction. Moreover, endothelial $Calr^{-/-}$ mice showed higher blood pressure, further supporting the role of endothelial Calr in blood pressure regulation (37).

Ca^{2+}-ATPase (SERCA)—Two isoforms of SERCA (SERCA2 and 3) were shown to be expressed in freshly dissociated ECs from coronary arteries and aorta (219), with SERCA3 described as the predominant isoform (304). In an early study, Liu et al. (263) generated $SERCA3^{-/-}$ mice and showed that endothelium-dependent vasodilation is impaired in these mice, although blood pressure was not affected. S100A1 is an intracellular Ca^{2+}-binding protein known to regulate SERCA activity (302, 303). $S100A1^{-/-}$ mice showed reduced NO production, impaired endothelium-dependent vasodilation, and higher blood pressure (363), suggesting that SERCA may be an essential regulator of eNOS activity and blood pressure. Consistent with this postulate, adenovirus-mediated SERCA2 delivery into coronary arteries of Yorkshire-Landrace swine increased eNOS activity. Similarly, an increase in eNOS activity was observed in cultured ECs from human coronary arteries infected with SERCA2-adenovirus (144). Li and colleagues (251) demonstrated that epicardial and endocardial ECs from mice treated with SERCA2-adenovirus are protected against Ca^{2+} overload-induced necroptosis known to occur during cardiac ischemia/reperfusion injury. Interestingly, a recent study by Zhang et al. (553) revealed a physical interaction between SERCA2 and PIEZO1 channel that results in suppression of PIEZO1 mechanosensation. The disruption of SERCA2-PIEZO1 interaction resulted in increased EC migration. It should be noted that the studies described above have been performed either in conduit arteries or in cell culture systems. Therefore, further investigation is needed to confirm the potential roles of different SERCA isoforms in regulating EC function in resistance arteries. In this regard, possible interactions between SERCA and other sources of Ca^{2+} in the endothelium will be particularly interesting.

Signaling Targets of Ca^{2+} in SMCs and ECs

Ca^{2+}-activated potassium channels

Large conductance Ca^{2+}-activated potassium (BK) channels in SMCs—BK channels have mostly been reported in SMCs, although a recent study suggested that functional BK channels are also present in native ECs (311). The unitary conductance of BK channels is 100 to 300 pS. BK channels are gated by membrane depolarization and intracellular binding to Ca^{2+} and Mg^{2+}. Yuan et al. (543) reported a complex structure of BK channels containing a functional pore formed by four α-subunits that represent

multiple splice variants of the Slo1 gene. Four accessory β subunits modulate channel activity. β1-subunit is the predominant β subunit in SMCs. Each α-subunit is composed of 11 hydrophobic segments (S0-S10) that form 3 main functional domains: the VSD, the cytosolic CSD, and the pore gate domain (PGD). The VSD is formed by S0-S4 TM segments and PGD is formed by TM S5-S6 and the P-loop, which confers selectivity for K^+. The remaining S7-S10 segments form the CSD and are located intracellularly. S4 helix is enriched with positively charged amino acids that constitute the channel voltage sensor. S0 helix is essential for bridging the α subunit with the β subunit, allowing β subunit-dependent channel modulation. The CSD comprises two potassium regulatory domains (RCK1 and RCK2), both containing putative high-affinity Ca^{2+}-binding sites. RCK2 Ca^{2+} biding site is called "Ca^{2+}-bowl" and includes a series of Asp residues. Finally, the binding site for Mg^{2+} is located at the interface between the VSD and CSD. The voltage sensitivity of BK channels is Ca^{2+}- and Mg^{2+}-independent. However, the interaction with Ca^{2+} and Mg^{2+} shifts the voltage-dependence of BK channels toward more negative potentials, allowing the channel to function under physiological condition (79, 469, 536). The Ca^{2+} bowl facilitates channel opening at low intracellular Ca^{2+} concentrations (<10 μM Ca^{2+}), whereas the RKC1 binding site influences activation over a broader range of Ca^{2+} concentrations (10–300 μM) (546).

BK channels are activated by RyR Ca^{2+} sparks in SMCs, resulting in SMC hyperpolarization and vasodilation (226). Therefore, BK channels are exposed to high local concentrations of intracellular Ca^{2+} (Ca^{2+} sparks 1–100 μM Ca^{2+}) (353). In this regard, β1 subunit is critical in enhancing the Ca^{2+} sensitivity of BK channels. Indeed, BK channels were uncoupled from Ca^{2+} sparks in SMCs from cerebral arteries of $\beta1^{-/-}$ mice. Consequently, myogenic vasoconstriction and blood pressure were significantly elevated in $\beta1^{-/-}$ mice (48, 267, 364). Isacson and colleagues (195) showed that the scaffolding protein receptor for activated C kinase 1 (RACK1) co-localizes with BK channels and slows BK channel activation in response to membrane depolarization. Further studies are needed to elucidate the physiological relevance of the RACK1-BK channel interaction.

Around 95% of α-subunits are found at the plasma membrane, whereas only a small percentage (10%) of β1 subunits are located at the plasma membrane. PKG and PKA enhance the trafficking of β1 subunits from the SR to the plasma membrane, increasing the open-state probability of BK channels and promoting vasodilation (248). Furthermore, PKG increases the open-state probability of BK channels via direct channel phosphorylation (387). In a recent study, Khavandi and colleagues (222) proposed a novel mechanism for indirect activation of BK channels by PKG. The authors reported that myogenic vasoconstriction generates H_2O_2, which activates PKG. PKG, in turn, enhances the activity of Ca^{2+} sparks and BK channels. PKA also increases BK channel activity through an indirect mechanism involving phosphorylation of phospholamban, causing SERCA disinhibition. Consequently, the increased SR Ca^{2+} load increases Ca^{2+} spark activity. Indeed, the effect of PKA on Ca^{2+} sparks and BK channels was impaired in phospholamban$^{-/-}$ mice (513). PKC, on the contrary, has an inhibitory effect on BK channel activity. Patch-clamp studies on freshly dissociated SMCs showed that PKC could directly inhibit BK channels independently of Ca^{2+} sparks (406). In guinea pig basilar arteries, β-adrenergic receptor stimulation activated BK channels via cAMP-dependent PKA

activation, in a PKG-independent manner (431). On the contrary, a separate study showed that β-adrenergic receptor stimulation of coronary arteries activates BK channels via PKG activation (517). Thus, the effects of protein kinases on BK channel activity are diverse and vary from one vascular bed to another.

GPCRs also alter BK channel activity via G protein-dependent and independent effects. Early studies showed that Ang II receptor 1 (AT1R) inhibited BK channel currents through a G protein-independent mechanism in coronary arteries (482, 555). Membrane-bound PIP2, which is regulated by GqPCR signaling, was shown to directly activate BK channels, thereby promoting the vasodilation of cerebral arteries (493). Fatty acids have also been documented to modulate BK channel activity. Ahn and colleagues (7) demonstrated that AA and long-chain fatty acids directly facilitate BK channel opening in rabbit coronary arteries. The BK channel opening effect was similar between saturated and unsaturated fatty acids. Docosahexaenoic acid (DHA), a polyunsaturated fatty acid (PUFA), evoked BK channel currents and vasodilation indirectly via its CYP metabolite 16,17-epoxydocosapentaenoic acid (505). In support of these findings, tail vein injection of a bolus of DHA lowered blood pressure, an effect that was absent in Slo1 deficient mice (181). In summary, the activity of BK channels is regulated by a plethora of endogenous mechanisms in vascular SMCs.

Intermediate and small conductance Ca^{2+} activated K^+ channels (IK/SK)

Endothelial cells (EC).: IK and SK channels have mostly been described in ECs. The unitary conductance of SK channels is approximately 10 pS, and that of IK channels is 20 to 30 pS. SK channel family is composed of four isoforms. SK1 (KCa2.1), SK2 (KCa2.2), and SK3 (KCa2.3) are encoded by KCNN1-3 genes, respectively. The fourth isoform, SK4 (IK or KCa3.1), shows higher conductance and is encoded by KCNN4 (6, 245). Functional SK/IK channel consists of four homologous subunits, each containing six TM segments (S1-6). Segments 5 and 6 line the pore-forming unit of the channel. S1 and S6 are connected to intracellular N- and C-terminal domains, respectively. SK/IK channels share a similar structure to voltage-gated K^+ channels (Kv) but do not exhibit voltage-dependence. This difference appears to be due to the diverse amino acid sequence of the S4 segment. Ca^{2+}-dependent activation of SK/IK channels does not rely on Ca^{2+}-binding directly onto the channel. Xia and colleagues (527) demonstrated that Ca^{2+} sensitivity of the channel is imparted by interaction with Ca^{2+}-CaM. The C-terminal lobe (C-lobe) of CaM associates with the C-terminal tail of SK channels in a Ca^{2+}-independent manner. The channel gate opens upon Ca^{2+} binding to the CaM N-lobe (407). Moreover, CaM binding to SK/IK channels is essential for channel assembly and trafficking to the plasma membrane (206). SK/IK channels show half-maximal activation response at similar Ca^{2+} concentrations (EC_{50} = 300–500 nM). Moreover, SK/IK channels display a fast time constant for activation (5–15 ms) (175, 527). This feature makes SK/IK channels an ideal target for coupling with distinct Ca^{2+} signals. Indeed, numerous studies have demonstrated that IK/SK channels are concentrated at MEPs in ECs, where the majority of localized Ca^{2+} signals also occur (20, 341, 342, 432, 433). Spatial proximity between SK/IK channels and Ca^{2+} signals at MEPs ensures selective activation of SK/IK channels by Ca^{2+} signals. SK/IK channel activation, in turn, results in EC membrane hyperpolarization, which is transmitted to SMC via MEGJs, causing vasodilation. SK and IK channel currents have been recorded in freshly isolated

ECs from mesenteric (432), cerebral (147), and pulmonary resistance (341) arteries. Taylor and colleagues (472) reported that SK3 channel deletion depolarizes EC membrane in mesenteric arteries and increases vasoconstriction and blood pressure. A subsequent study showed that inhibition of SK or IK channels depolarizes ECs from mesenteric arteries by approximately 8 and 3 mV, respectively (242). These results suggest that SK/IK channels might be constitutively activated by spontaneously occurring Ca^{2+} signals in ECs.

Smooth muscle cells (SMC).: IK channels have been shown to be involved in SMC dedifferentiation and proliferation (131, 229, 320). Tharp et al. (475) showed that platelet-derived growth factor-BB (PDGF-BB) increased functional IK channels in SMCs from swine coronary arteries. Moreover, increased IK channel activity reduced the expression of SMC differentiation markers. Overexpression of IK channels in non-proliferating SMCs promoted dedifferentiation and proliferation by creating the electrochemical gradient favoring Ca^{2+} influx. Increased intracellular Ca^{2+} activated cAMP response element-binding protein (CREB), a mitogen-induced transcriptional factor, thereby driving SMC proliferation (34). Augmented IK channel transcription in proliferating SMCs was attributed to reduced expression of repressor element 1-silencing transcription factor (REST) (69). IK channel inhibition decreased SMC proliferation in response to growth factors (131, 475), further supporting the role of IK channels in SMC proliferation. Gole and colleagues (131) proposed that fibroblast growth factor induces IK channel upregulation via NOX5-dependent ROS production in SMCs from porcine coronary arteries. Of particular clinical importance is the finding that IK channel inhibition was protective against restenosis in the rat (229) and swine models (476). Moreover, genetic deletion and pharmacological inhibition of IK channels was protective against atherosclerosis in a mouse model (486). The substantial evidence supporting a crucial role of IK channels in SMC proliferation suggests that IK channels could be therapeutically targeted in vascular lesions linked to SMC proliferation. However, the central role of IK channels in endothelium-dependent vasodilation may prove problematic with this approach.

Protein kinases

Ca^{2+}-CaM-dependent protein kinase II (CaMKII)

Endothelial cells (EC).: Ser or Thr residues are the target sites of phosphorylation by Ca^{2+}-CaM kinase family (CaMK); therefore, CaMKs are also known as Ser/Thr kinases. CaMKs share a conserved structure with three characteristic domains: catalytic, autoinhibitory, and CaM-binding domains. CaMK family is divided into two main groups—multifunctional CaMKs (CaMKI, CaMKII, and CaMKIV), which have multiple downstream intracellular targets; and substrate-specific CaMKIII, which has only one downstream target (350). CaMKII has recently emerged as an essential vasoregulatory mechanism. CaMKII is expressed as one of the four isoforms (α, β, δ, and γ), with a and β isoforms occurring primarily in the brain and δ and γ isoforms expressed in blood vessels (481). CaMKII, unlike other CaMKs, does not exist in a monomeric state. Indeed, CaMKII has a peculiar association domain that allows the multimeric association of 6-12 monomers, which is partly responsible for the ability of CaMKII to respond to diverse intracellular Ca^{2+} oscillations (455). Activation of CaMKII occurs in multiple steps. The first step (Ca^{2+}-CaM-dependent) involves Ca^{2+}-CaM binding to CaMKII and disrupts the interaction between

the autoinhibitory and catalytic domains. In the second step (Ca^{2+}-CaM independent), the Ca^{2+}-CaM activated subunit phosphorylates the catalytic subunit and activates it (77).

The significance of CaMKII in orchestrating the functional responses to intracellular Ca^{2+} is unclear, mainly due to two reasons (i) the majority of studies on CaMKII have been performed in cell culture systems and evidence from intact tissue is scarce (485); and (ii) numerous studies have used KN-93, a non-specific CaMKII inhibitor (351). Therefore, caution must be used while interpreting the currently available literature on CaMKII. In a recent development, Murthy and colleagues (307) investigated the role of CaMKII *in vivo* using a transgenic mouse model, where AC3-I (CaMKII inhibitory peptide) was conditionally expressed in the endothelium. AC3-I mice showed unaltered circulating NO levels and blood pressure compared to control mice. Furthermore, endothelium-dependent vasodilation of mesenteric arteries was also unchanged in AC3-I mice. However, in culture systems, AC3-I-dependent CaMKII inhibition prevented the increase in intracellular Ca^{2+} in response to bradykinin. Therefore, further evidence is needed for a definitive assessment of the functional roles of CaMKs in ECs.

Smooth muscle cells (SMC).: The involvement of CaMKII in SMC proliferation and migration has mainly been studied in cell culture systems and conduit arteries, and therefore, will not be discussed in this article. Ledoux and colleagues (243) recently postulated that CaMKII facilitates LTCC activity by exerting rapid positive feedback on LTCC currents in SMCs. As acknowledged by the authors, this study used non-specific CaMKII inhibitor KN-93 (124, 243, 384). Prasad and colleagues (372) developed a novel mouse model that conditionally expresses specific CaMKII peptide inhibitor CaM-KIIN (TG SM-CaMKIIN mice) in SMCs. TG SM-CaMKIIN mice showed reduced CaMKII-dependent phosphorylation of LTCC channel β3 subunit and phospholamban, resulting in lower LTCC channel currents and reduced SERCA activity. Furthermore, Ang II- and phenylephrine-induced increase in intracellular Ca^{2+} was attenuated in TG SM-CaMKIIN mice, although Ang II- and phenylephrine-evoked vasoconstriction was not altered. Interestingly, TG SM-CaMKIIN mice showed reduced CaMKII-dependent inhibition of MLCK, which was proposed as a compensatory mechanism that normalized Ang II- and phenylephrine-evoked vasoconstriction. In a subsequent study, Prasad et al. (371) demonstrated that chronic Ang II infusion in TG SM-CaMKIIN mice leads to higher mesenteric artery remodeling. These findings propose an exciting paradigm where CaMKII, *per se,* does not alter vasoconstriction, but by limiting vascular hypertrophy, may prevent the damaging effects of long-term hypertension.

Protein kinase C (PKC)—This large family of serine/threonine protein kinases has been divided into four functionally diverse subfamilies according to their enzymatic properties. PKCα, PKCβ, and PKCγ belong to the conventional family (cPKC). This article will specifically focus on cPKCs as they are activated in a Ca^{2+}-dependent manner (290). The remaining families are novel PKCs (nPKCs) composed of the δ, η, ε, and θ isotypes; atypical PKCs (aPKCs) λ and ζ; and the protein kinase C-related kinase (PRK) family. The enzymatic activity of nPKCs and aPKCS is Ca^{2+} independent (390). PKC is activated by

DAG (463), phosphatidylserine (PS) (426), and by phorbol 12-myristate 13-acetate (PMA) (53).

The N-terminal regulatory (36 kDa) and C-terminal catalytic domains (42 kDa) of PKC are separated by a hinge region (224). The regulatory domain contains (i) a cysteine-rich sequence that coordinates two Zn^{2+} ions (439) and is essential for DAG, PMA (339, 424, 439), and PS binding (223, 319); (ii) a conserved autoinhibitory sequence (183) that maintains PKC in an inactive state in the cytosol (184); and (iii) a CBD (230). Ca^{2+} binding is a pivotal step for PKC activation and its membrane association. Binding of cytosolic PKC with two Ca^{2+} ions results in a weak association with the plasma membrane, whereas interaction of PKC with the third Ca^{2+} ion enables its strong association with the plasma membrane (230). The Ca^{2+}-bound form of PKC is also required for its interaction with PIP2 (399). The catalytic domain comprises ATP binding sequence and a region important for PKC-substrate interaction (329). PKC activators, including Ca^{2+}, DAG, PS, and PMA, promote complete allosteric activation and translocation to the plasma membrane (386).

Endothelial cells (EC).: PKC has been shown to promote EC proliferation by participating in the vascular endothelial growth factor (VEGF) signaling cascade (524). PKCβ is thought to be the main isoform associated with the mitogenic effects of VEGF (8, 526), although PKCα has also been associated with VEGF-induced angiogenesis (514). Suzuma et al. (453) demonstrated that PKCβII promotes retinal neovascularization in a mouse model of oxygen-induced retinal neovascularization. Indeed, retinal neovascularization was diminished in $PKC\beta^{-/-}$ mice, whereas a more extensive network of neovascularization was observed in a mouse model overexpressing PKCβII (PKCβII Tg) (453). On the contrary, a separate study by Spyridopoulos and colleagues (436) reported that specific PKCα and PKCβ inhibition increases VEGF-induced angiogenesis. In this study, PKCα and PKCβ inhibition also enhanced the VEGF-dependent increase in vascular permeability via NOS activation. The reasons for the conflicting results in the two studies (436, 453) remain unclear.

Adapala et al. (3) demonstrated that PKCα is necessary for acetylcholine-induced Ca^{2+} entry via TRPV4 channels. Further studies by Sonkusare and colleagues demonstrated that PKC anchoring by AKAP150 is necessary for enhancing Ca^{2+} influx through TRPV4 channels at MEPs. In this regard, Fan et al. (111) showed that PKC phosphorylates TRPV4 channels, an effect that is enhanced by the presence of AKAP150. Along similar lines, Ottolini et al. (343) demonstrated that acetylcholine- and PKC-activation of TRPV4 channels were absent in endothelium-specific $TRPV4^{-/-}$ mice. However, cell-specific knockout mice are needed to obtain an accurate understanding of the relative contributions of different PKC isoforms to vascular function.

Smooth muscle cells (SMC).: DAG- or Ca^{2+}-activation of PKC promotes SMC contractility via a multitude of mechanisms (17). SMC contractility was enhanced following PKC-dependent inhibition of myosin light chain phosphatase (MLCP) activity (225, 521). Moreover, PKC activation had an inhibitory effect on BK channel currents in SMCs from rat mesenteric arteries (457), rat pulmonary arteries (26), and cat cerebral arteries (240). In SMC isolated from rabbit coronary arteries, Ang II-induced inhibition of the inward rectifier K^+ (K_{ir}) channel current was also mediated by PKCα (346). Kanashiro and colleagues

(211) showed that PKCα mediated eicosanoid-induced vasoconstriction of porcine coronary arteries. In pressurized rat cerebral arteries, PKC inhibition impaired myogenic vasoconstriction (425), suggesting an essential role for PKC in the development of myogenic vasoconstriction. It was suggested that PKC might favor myogenic vasoconstriction through its actions on the cytoskeletal organization. Specifically, by phosphorylating the heat shock protein 27 (HSP27), PKC reduced SMC G-actin content and favored actin polymerization, promoting force generation during myogenic vasoconstriction (301). Consistent with these *ex vivo* findings, Wynne et al. showed that global PKCα$^{-/-}$ mice have lower resting blood pressure (301).

Myosin light-chain kinase (MLCK)—MLCK is a Ca^{2+}/CaM-dependent kinase that promotes actin-myosin cross-bridge formation and vasoconstriction (429) (Figure 1). PKA-dependent phosphorylation on Ser^{512} negatively modulates the Ca^{2+}/CaM-sensitivity of MLCK (191, 271) and reduces its affinity for Ca^{2+}/CaM (Ca^{2+} desensitization) (74). CaMKII also appears to be involved in MLCK phosphorylation and Ca^{2+} desensitization (470, 471). Two different genes encode for MLCKs: smooth muscle MLCK (*mylk1* (123) and skeletal muscle MLCK (*mylk2*) (169, 209). For this article, we will focus on SMC MLCK and will refer to it as MLCK. Two known isoforms of MLCK are: short MLCK (130–150 kDa), which is expressed in mature SMCs (43); and long MLCK (208–214 kDa), which is expressed mainly in embryonic SMCs (209) and mature ECs (498).

Endothelial cells (EC).: The phosphorylation status of myosin light chain (MLC) is an essential regulator of EC permeability. MLCK enhances actomyosin contractility and weakens EC-EC adhesion by phosphorylating MLC (94, 479, 480). Thus, MLCK-dependent MLC phosphorylation regulates endothelial barrier function by maintaining a basal degree of permeability. Indeed, MLCK inhibition resulted in reduced vascular permeability (544). Huang et al. (187) showed that MLCK inhibition lowers microvascular hyperpermeability in thermal injury. Genetic deletion of the long MLKC isoform (MLCK-210$^{-/-}$) confirmed the importance of long MLKC in increasing the pulmonary microvascular permeability in response to lung injury (503). Moreover, MLCK-210$^{-/-}$ mice are protected against microvascular hyperpermeability induced by burn injury (383). Moitra and colleagues (297) generated genetically engineered mice overexpressing the long MLKC isoform in ECs (VE-MLCK-210). VE-MLCK-210 mice showed increased pulmonary microvascular permeability under resting conditions and augmented hyperpermeability following lung injury (297). These findings established a pivotal role for long MLKC in increasing microvascular permeability. Therefore, targeting long MLKC isoform may be a promising therapeutic intervention in pathological conditions characterized by increased microvascular leakage. In this regard, further research on developing isoform-specific MLKC inhibitors is needed to reduce possible side effects with inhibition of long MLCK (413).

Smooth muscle cells (SMC).: MLCK initiates SMC contraction by phosphorylating Ser^{19} of the myosin II RLC. Phosphorylation of RLC activates actomyosin ATPase, which turns on cross-bridge cycling and promotes force development (208, 445). Indeed, SMC-specific MLCK deletion resulted in reduced vasoconstriction and lower blood pressure (164). In a recent study, Chen et al. (62) created a mouse model with SMC-specific deletion of short

MLCK. These mice showed reduced contractility of gastrointestinal SMCs, suggesting that short MLCK is essential for gastrointestinal smooth muscle contractility (62). To the best of our knowledge, vascular contractility studies have not been performed in this mouse model.

Endothelial nitric oxide synthase (eNOS)

NO was first identified as the major endothelium-derived relaxing factor nearly 30 years ago (120, 121, 188, 189, 306). To this date, NO-dependent vasodilation remains the most studied mechanism for endothelium-dependent vasodilation under physiological and pathological conditions. Three different nitric oxide synthases (NOSs) catalyze the production of NO from L-arginine—neuronal or nNOS; inducible or iNOS; and endothelial or eNOS (116). Although other NOS can be present in the vascular wall, endothelial NO mainly comes from the activation of eNOS or NOS3 (11, 298, 496). Synthesis of NO by eNOS requires the precursor L-arginine, cofactors tetrahydrobiopterin (BH4), flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), CaM, and iron protoporphyrin IX (Heme Fe). eNOS protein is synthesized as monomers but needs to form homodimers to produce NO. As monomers, the oxygenase domain of eNOS produces superoxide; a phenomenon commonly referred to as eNOS uncoupling that contributes to oxidative stress in diseases (496).

eNOS is localized in the caveolae, which are membrane invaginations rich in caveolin-1 (116, 434). eNOS can be activated in a Ca^{2+}-dependent manner or through posttranslational modifications. Ca^{2+} can activate eNOS by inducing CaM binding to the CaM-binding domain on eNOS. Increased Ca^{2+}-CaM displaces eNOS from caveolin-1 and relieves the inhibitory effect of caveolin-1 on eNOS activity (88). Moreover, the displacement of eNOS from caveolin-1 promotes its translocation to the cytosol, where eNOS can undergo posttranslational modifications that activate it. Association of eNOS with caveolin-1 also localizes it with several other signaling molecules, including ion channels, protein kinases, GPCRs, and tyrosine kinases, thus potentially increasing the chances of eNOS activation by these signaling elements (496).

Phosphorylation can have variable effects on eNOS activity depending on the site of phosphorylation. Phosphorylation at Ser^{1177} activates, whereas phosphorylation at Thr^{495} inhibits the enzyme (115, 116, 167, 293). PKA, PKB, AMPK, CaMK, and ERKs 1 or 2 can phosphorylate eNOS at Ser^{1177} (167). On the contrary, Rho kinase and PKC phosphorylate eNOS at Thr^{495} and thus inhibit it (61, 446). Moreover, tyrosine kinase can also phosphorylate eNOS on Tyr^{657} and lower eNOS activity (114). Phosphorylation of eNOS at Tyr^{81} by Src kinase facilitates NO production (119). In addition to phosphorylation, other posttranslational modifications that modify eNOS activity include cysteine palmitoylation, which localizes eNOS to the caveolae and brings it closer to regulatory signaling elements (262); S-nitrosylation at Cys^{94} and Cys^{99} that inhibits enzyme activity (379); acetylation at Lys610 and deacetylation at Lys^{497} and Lys^{507}, which increase the enzyme activity (167); glycosylation at Ser^{1177}, which decreases eNOS activity (308); S-glutathionylation at Cys^{689} and Cys^{908}, which promotes eNOS uncoupling (59, 60).

NO released as a result of eNOS activation can passively diffuse to the SMC layer, where it activates a soluble GC-cGMP-PKG signaling pathway to cause vasodilation (86). NO can also activate the endothelial GC-PKG pathway that limits Ca^{2+} influx in ECs

and endothelium-dependent vasodilation (282). Two main K^+ channels that regulate SMC membrane potential are BK and Kv channels (201). While it is well established that NO activates both BK and Kv channels, the mechanism of activation appears to be twofold. Some studies show GC-cGMP-dependent activation of BK channels by NO (18, 387), whereas other studies indicate that NO can activate both BK and Kv channels in a GC-PKG-independent manner (45, 295). The latter mechanism possibly involves post-translational modification of the channel by NO, such as S-nitrosylation, or cAMP-PKA signaling (194). Activation of SMC K^+ channels by NO results in membrane hyperpolarization, which deactivates LTCCs to relax SMCs. PKG also promotes the uptake of Ca^{2+} by the SR by phosphorylating phospholamban, which increases SERCA activity (52, 496). IP3R Ca^{2+} release from the SR in SMCs is crucial for myogenic vasoconstriction (132, 516). PKG has also been shown to phosphorylate IP3R-associated PKG substrate (IRAG), inhibiting Ca^{2+} release from the SR (402, 403) and myogenic vasoconstriction. The NO-GC-cGMP-PKG-I pathway also activates MLCP in SMCs. PKG-I binds to and phosphorylates the regulatory subunit of MLCP, MYPT1, and prevents the inhibition of MLCP. This MLCP de-inhibition lowers cross-bridge cycling and SMC contraction (258, 452, 522).

Intriguingly, both IK/SK channels and eNOS can be activated by Ca^{2+}, and yet either eNOS or IK/SK channels play a predominant role in endothelium-dependent vasodilation in each vascular bed. A generally accepted distinction is that eNOS regulates endothelium-dependent vasodilation in larger (conduit) arteries, whereas IK/SK channel-mediated hyperpolarization plays a major role in smaller, resistance-sized arteries (419, 492). Moreover, lower level, localized increases in Ca^{2+} seem to preferentially couple with IK/SK channels (20, 178, 432, 433) except in the case of small pulmonary arteries where they couple with eNOS (282). Ottolini and colleagues (341) recently showed that Ca^{2+} signal-IK/SK channel co-localization and NO scavenging protein Hbα favor Ca^{2+}-IK/SK channel signaling in systemic arteries. On the contrary, Ca^{2+} signal-eNOS co-localization and absence of Hbα facilitated Ca^{2+} signal-eNOS signaling in the pulmonary circulation (Figure 7). It should be noted that the blood pressure is elevated in eNOS global knockout mice (414, 438, 494). eNOS is also expressed in cell types other than ECs. Therefore, investigations in endothelium-specific $eNOS^{-/-}$ are likely to result in interesting findings on endothelium-dependent vasodilation and blood pressure regulation.

Arterial and Arteriolar Ca^{2+} Signaling in Vascular Disorders

The role of abnormal Ca^{2+} signaling mechanisms in the pathogenesis of vascular disorders is well established, particularly in resistance-sized arteries and arterioles. Both endothelial and SMC Ca^{2+} signaling mechanisms are impaired in various disorders. Ca^{2+} signals in SMCs have mostly been associated with increased in activity, resulting in vasoconstriction and higher vascular resistance. RyR-mediated Ca^{2+} sparks are an exception to this rule as they are vasodilatory signals, and their activity is decreased in vascular disorders. Impairment of endothelial Ca^{2+} signaling mechanisms attenuates endothelium-dependent vasodilation, contributing to increased vasoconstriction in vascular disorders. Increased activity of SMC and endothelial Ca^{2+} signals has also been associated with hyperproliferation, migration, and hyperpermeability in vascular disorders. In this section, we will discuss the studies on Ca^{2+} signaling mechanisms in resistance arteries and arterioles in vascular disorders.

Abnormal Ca^{2+} signaling in SMCs

SMCs from small mesenteric arteries of hypertensive rats showed higher LTCC current density and a leftward shift in the voltage-dependence of LTCC activation. Furthermore, a linear correlation was observed between systolic blood pressure and LTCC current density (269). Notably, treatment of hypertensive rats with angiotensin-converting enzyme (ACE) inhibitor normalized LTCC currents and reduced blood pressure (80). Bannister and colleagues (25) demonstrated that increased expression of auxiliary LTCC subunits α2δ-1 in cerebral arteries from spontaneously hypertensive rats (SHRs) promotes LTCC channel trafficking to the membrane and increases LTCC currents. An increase in SMC LTCC density has also been reported in non-genetic models of hypertension (423). In an Ang II-induced hypertension model, the increase in LTCC currents was associated with the upregulation of β3 regulatory subunit and increased translocation of pore-forming α1C subunit to the membrane (221). Intriguingly, Tajada and colleagues (458) reported lower number of LTCCs, but highly active subpopulations of LTCCs in a mouse model of essential hypertension. These findings support the idea that localized, as opposed to wholecell, changes in intracellular Ca^{2+} may be a more accurate readout of pathological outcomes. In this regard, Nieves-Cintron and colleagues showed that AKAP150 anchoring of PKCα in the vicinity of LTCCs created microdomains of increased LTCC activity. Indeed, AKAP150$^{-/-}$ and PKCα$^{-/-}$ mice were protected against Ang II-induced hypertension (316). AKAP150 also anchors calcineurin (323), which is excessively activated by Ca^{2+} influx through LTCC in hypertension and diabetes (16, 335). LTCC-mediated activation of calcineurin dephosphorylated NFATc3, resulting in its translocation to the nucleus, where it downregulated BK channel β1 subunit (324). Reduced β1 subunit expression impaired the activity of BK channels and elevated blood pressure (335, 364). Excessive LTCC activation has also been demonstrated in cerebral arteries from a mouse model of type 2 diabetes (317) and a rat model of subarachnoid hemorrhage (336). Thus, evidence in the literature strongly supports the concept that increased LTCC activity in SMCs contributes to elevated vasoconstriction in vascular disorders.

Abnormalities of SMC Ca^{2+} signaling mechanisms have also been reported in pulmonary SMCs. The upregulation of SMC LTCCs was shown to contribute to hypoxia-induced pulmonary hypertension (174). Recent studies by Jernigan and colleagues identified acid-sensing ion channel-1 (ASIC1) overexpression as a novel mechanism for elevated SMC Ca^{2+} in hypoxic pulmonary hypertension (134). In a subsequent study, Jernigan and colleagues showed that RhoA increases the plasma membrane localization of ASIC1 in SMCs. In this regard, the scaffolding protein interacting with C-kinase-1 (PICK1) (252, 508) interacts with ASIC1 (186). Furthermore, Herbert et al. (168) showed that PICK1 anchors calcineurin close to ASIC1, promoting dephosphorylation of and Ca^{2+} entry through ASIC1 in SMCs from pulmonary arteries. Based on these results, PICK1-calcineurin-ASIC1 interaction may represent a novel signaling pathway that augments SMC Ca^{2+} in pulmonary hypertension.

In a separate study, Yuan and colleagues demonstrated that TRPC1 channels increase pulmonary vasoconstriction through capacitative Ca^{2+} entry (235) and are upregulated in pulmonary arterial hypertension (542). In a chronic hypoxic mouse model of pulmonary

hypertension, Sham and colleagues showed that the SMC TRPV4 channel is upregulated and contributes to increased pulmonary artery vasoconstriction (528, 538). Thus, abnormalities in voltage-gated and non-voltage-gated Ca^{2+} channels on SMC membranes have been shown to contribute to pulmonary vasoconstriction in pulmonary hypertension.

Abnormal Ca^{2+} sparks-BK channel coupling has been proposed as a contributor to vascular dysfunction. Angiotensin II-induced hypertension caused a pathological downregulation of β1-subunit of the BK channel, resulting in the uncoupling of BK channels from Ca^{2+} sparks (15). Consistent with these findings, a gain-of-function point mutation on *KCNMB1* (gene encoding for β1 subunit) was protective against diastolic hypertension (112). Pritchard and colleagues (374) identified the effects of Duchenne muscular dystrophy (DMD) on Ca^{2+} events in SMCs from cerebral arteries. In this study, the cluster size of RyRs, which co-localize with BK channels at the plasma membrane, was significantly larger in DMD mice. A higher number of RyRs within a cluster increased "Ca^{2+}-induced Ca^{2+}-release" and elevated the probability of Ca^{2+} spark occurrence. The abnormally high Ca^{2+} spark-BK channel signaling resulted in impaired myogenic vasoconstriction. On the contrary, the expression of RyRs was reduced in cerebral arteries from db/db mice, resulting in impaired Ca^{2+} sparks-BK channel signaling (392). In a recent study, Nieves-Cintrón and colleagues (325) observed that reduced functional coupling between α and β1 subunits of BK channels contributed to higher vasoconstriction in patients with type 2 diabetes.

SMC NCX1 appears to be a substantial contributor to the pathogenesis of salt-sensitive hypertension. A high-salt diet augments the production of cardiotonic steroids (CTS). CTS inhibited Na^+/K^+ ATPase and led to a pathological increase in intracellular Na^+ (146, 160). Under these conditions, NCX1 worked in the reverse mode and caused SMC Ca^{2+} overload. Consistent with these findings, SMC-specific $NCX1^{-/-}$ mice were protected against salt-induced hypertension (509). Moreover, SMC-specific NCX1 overexpression worsened high-salt diet-induced hypertension (199). Therefore, NCX1-dependent signaling could be therapeutically targeted in salt-sensitive hypertension.

SMC IP3Rs were involved in increased phenylephrine (α1AR agonist)-induced vasoconstriction of femoral arteries from rats with heart failure (231). Moreover, Ang II-induced NFAT activation increased IP3R expression in SMCs, resulting in exaggerated vasoconstriction (2). Along similar lines, SMCs from mesenteric arteries of hypertensive rats showed increased ET-1 induced contraction due to enhanced spatial coupling between IP3R1 and TRPC3 channels (4). Preglomerular microvascular smooth muscle cells (PGVMSCs) from SHRs showed augmented Ang II- and neuropeptide Y1-induced proliferation due to excessive IP3R activation (65, 563). This effect was attributed to increased plasma membrane localization of RACK1. RACK1 facilitated the proximity of PLC to AT1R and neuropeptide Y1-receptor, thereby facilitating PLC-IP3R signaling (65, 563). RACK1 can also directly activate IP3Rs, resulting in PGVMSC proliferation (64, 349). Use of SMC-specific RACK1 knockout mice will provide a definitive answer on the role of RACK1 in influencing SMC function. In summary, multiple studies support a pathological role for SMC IP3Rs in vascular disorders.

Abnormal Ca^{2+} signaling in ECs

In the endothelium, AKAP150 and TRPV4 channels are highly localized at MEPs, where AKAP150 anchors PKC in the vicinity of TRPV4 channels and increases the coupling among TRPV4 channels (433). Ca^{2+} influx through endothelial TRPV4 channels causes vasodilation via IK/SK channel activation (20, 432). Sonkusare and colleagues (433) demonstrated that Ang II-induced hypertension disrupts endothelial AKAP150-TRPV4 channel signaling by lowering the expression of AKAP150 at MEPs. A recent study by Ottolini et al. (342) proposed the concept of pathological signaling microdomains in obesity, whereby pathological elements localized at MEPs impaired endothelial Ca^{2+} signaling. The authors first demonstrated the importance of endothelial AKAP150-TRPV4 channel signaling in lowering systemic blood pressure under normal conditions. In obesity, increased expression of inducible nitric oxide synthase (iNOS) and NADPH oxidase 1 (NOX1) at MEPs correlated with elevated levels of NO and superoxide radicals (O_2^{-}), respectively. Interaction of NO and $O_2^{-\cdot}$ resulted in localized formation of the oxidant molecule peroxynitrite. Peroxynitrite, in turn, disrupted AKAP150-PKC interaction, thereby reducing TRPV4 channel activity at MEPs. The loss of endothelium-dependent vasodilation, as a result of this pathological signaling, led to increased blood pressure in obesity. In a separate study, Wilson and colleagues (520) indicated that altered Ca^{2+} signaling networks of ECs contribute to the loss of endothelial function in obesity. Ca^{2+} signaling networks of ECs are critical for determining overall vascular resistance (246). While the loss of endothelial function in obesity is well documented (342, 520), a study by Greenstein and colleagues (139) reported that obesity is not associated with a loss of endothelium-dependent vasodilation. Differences in diet regimens and analytical techniques may be responsible for the divergent findings. Regardless, it should also be noted that obesity-induced vascular dysfunction is multifactorial and likely caused by both endothelial and smooth muscle impairments.

Alterations in Ca^{2+} signals through endothelial TRPV4 channels have been demonstrated in multiple disease models. In cerebral arteries from a mouse model of Alzheimer's disease, endothelial TRPV4 channel activity was impaired with a consequent decrease in acetylcholine-evoked vasodilation. The impairment of TRPV4 channel activity was linked to the excessive formation of ROS in this model. Indeed, reducing H_2O_2 and O_2^{-} levels rescued the vasodilation to acetylcholine (552). Similarly, Ma et al. (272) observed decreased acetylcholine-induced vasodilation in mesenteric arteries from diabetic mice that was attributed to impaired TRPV4-SK channel signaling. Stroke-prone SHRs also showed a downregulation of endothelial TRPV4 and SK channels, resulting in impaired acetylcholine-induced vasodilation (408).

Recent discoveries suggest a detrimental role for excessive Ca^{2+} in ECs from arteries or capillaries in the pathogenesis of some vascular disorders. Excessive endothelial Ca^{2+} activity in systemic arteries was correlated with elevated histone levels after traumatic brain injury (73). Collier and colleagues (73) found that high levels of histones in the plasma from trauma patients evoked an exaggerated increase in endothelial Ca^{2+}. Prolonged exposure to histones led to endothelial Ca^{2+} overload, EC death, and subsequent loss of endothelium-dependent vasodilation. Another study by Suresh et al. (450) suggested that

higher endothelial Ca^{2+} levels, resulting from increased TRPV4 channel activity, underlies capillary endothelial migration in pulmonary hypertension. Contrary to these results, a recent study presented an exciting idea that reduced membrane cholesterol content lowers Ca^{2+} entry in ECs in pulmonary hypertension (548).

Methodologies for Recording Ca^{2+} signals in SMCs and ECs

Ca^{2+} signals within the cells have unique spatiotemporal properties that translate into numerous cellular functions (31). Therefore, the diversity of Ca^{2+} signals cannot be captured with one technique. However, over the last two decades, the use of sensitive fluorescent Ca^{2+} indicators and fast, high-resolution imaging techniques (confocal, total internal reflection fluorescence or TIRF, and multi-photon imaging) have enabled effective spatiotemporal resolution of individual Ca^{2+} signals. Fluorescent indicators are synthesized as membrane-permeable acetoxymethyl (AM) esters. Cytosolic esterases release the anionic cell impermeable form, which remains in the cytosol (491). Fluorescent Ca^{2+} indicators can be classified into ratiometric (dual-wavelength) and non-ratiometric (single wavelength) indicators. Ratiometric indicators show a shift in their excitation (Fura-2) or emission (Indo-1) spectrum upon Ca^{2+} binding. A classic example of ratiometric indicators is Fura-2, which presents two excitation wavelengths (Ca^{2+}-free form/Ca^{2+}-bound form = 380/340 nm). Elevation in cytosolic Ca^{2+} levels increases Fura-2 fluorescence at 340 nm (Ca^{2+}-bound form) and decreases the fluorescence at 380 nm (Ca^{2+}-free form). Therefore, the ratio of the emission intensity at 340 nm to that at 380 nm is proportional to cytosolic Ca^{2+} concentration. Ratiometric dyes have mostly been used for quantification of whole-cell changes in Ca^{2+} concentration. Non-ratiometric indicators (fluo-indicators), on the contrary, do not show a shift in excitation/emission wavelengths upon Ca^{2+} binding. Instead, the fluorescence intensity increases upon Ca^{2+} binding (140). Usually, fluorescence values of non-ratiometric indicators are presented as a ratio between the fluorescent value during the occurrence of a Ca^{2+} signal (F) and that at the baseline (F_0, no Ca^{2+} activity) (294). The use of ratiometric indicators is not associated with loading and photobleaching issues that are commonly experienced with non-ratiometric indicators. The drawbacks of ratiometric indicators are (i) they are not suitable for capturing fast, spatially restricted Ca^{2+} signals; (ii) they require excitation with ultraviolet light, which is harmful to biological samples; and (iii) they cannot be used for studies of individual fast Ca^{2+} signals. Moreover, ultraviolet light is not effectively transmitted through most high numerical aperture objectives. Therefore, non-ratiometric indicators are the “gold standard” for studying fast, spatially restricted Ca^{2+} signals (sparks, sparklets, etc.). The main drawbacks of these indicators are uneven sample loading, photobleaching, and leakage issues. Photobleaching occurs when the indicator, in the excited form, undergoes oxidation by interacting with molecular oxygen. Therefore, lowering the laser intensity can prevent photobleaching (477). Non-ratiometric indicators can compartmentalize to specific intracellular organelles. Blocking of anionic-organic cellular transporters has been used as a strategy to reduce this phenomenon (90). Moreover, determining the optimum duration for dye-loading can lower the risk of uneven loading or overloading of the sample.

The selection criteria for Ca^{2+} indicators should include the concentration range of Ca^{2+} signals being recorded. In an ideal scenario, the mid-point of Ca^{2+} concentration range is

close to the dissociation constant (K_d) of the indicator. Indicators with high K_d (low Ca^{2+} affinity) are suitable for detecting large increases in Ca^{2+}. In contrast, indicators with low K_d (high Ca^{2+} affinity) are better suited for detecting lower levels of Ca^{2+} and become saturated at high Ca^{2+} concentrations. Indeed, some localization studies of Ca^{2+} entry events have used a combination of low- and high-affinity Ca^{2+} indicators. A combination of Fluo-5 (K_d = 2.3 μM) and an excess of non-fluorescent EGTA (K_d = 150 nM) was used to study the initiation sites of LTCC sparklets (315). The Ca^{2+}-binding rate ($K_{on} = K_{off}/K_d$) of Fluo-5 is 100-times faster than that of EGTA. Therefore, Fluo-5 can detect the more recent Ca^{2+} ions that have entered into the cell before ceding them to EGTA. The combination of Fluo-5 and EGTA allowed the identification of Ca^{2+} entry sites, which are expected to be within 50 and a few hundred nanometers from the fluorescence signal (110, 292, 315, 547). The combination of Fluo-4 (K_d = 335 nM) and EGTA was used by Sonkusare and colleagues (433) to decipher Ca^{2+}-dependent potentiation of endothelial TRPV4 channels in a cluster. EGTA chelates intracellular Ca^{2+} and was found to disrupt Ca^{2+}-dependent channel to channel communication.

Genetically encoded Ca^{2+} indicators (GECIs) have proved immensely helpful for studying Ca^{2+} signals in biological systems. GECI are encoded by engineered DNA sequences that can be incorporated into the cell genome. Indeed, combining GECI with cell-specific promoters results in cell-specific expression of the Ca^{2+} biosensor proteins, which constitutes an enormous advantage over the use of fluorescent indicators. Ca^{2+} indicators can show undesirable compartmentalization to intracellular organelles and get pumped out from the cell by ATPases at the cell membrane. GECIs are devoid of these disadvantages. The most popular GECI is GCaMP. Briefly, GCaMP protein is formed by a circularly permutated version of GFP (cpGFP) fused with CaM and CaM-interacting MLCK M13 peptide. Ca^{2+} biding with CaM causes a conformational change in cpGFP and results in a substantial increase in fluorescence. Point mutations on the GCaMP amino acid sequence have yielded different GCaMP generations with improved dynamic range, kinetic properties, and Ca^{2+} sensitivity. In the vascular field, mice expressing GCaMP under the connexin40 (Cx40) promoter or acta2 promoter have been engineered to study Ca^{2+} events restricted to endothelium (244, 432, 468) or SMCs (421), respectively.

Conclusions

Ca^{2+} signals in SMCs and ECs arise from different sources and couple with disparate targets. Various Ca^{2+} signals combined with multiple Ca^{2+}-sensitive targets and physiological stimuli result in numerous stimulus-Ca^{2+} signal-target linkages and functional effects. Ca^{2+} signals in ECs and SMCs occur in a spatially restricted manner; however, excessive activation of individual signals can result in a whole-cell increase in Ca^{2+}. Ca^{2+} influx is mediated by voltage-gated and non-voltage-gated (both SMCs and ECs) Ca^{2+} entry pathways. Voltage-gated ion channels play a crucial role in SMCs, but their functional expression has not been shown in the intact endothelium. Recent developments in image acquisition speed, combined with confocal, TIRF, and multi-photon imaging, have advanced our understanding of spatial and kinetic properties of the individual Ca^{2+} signals in the vasculature. Recent functional studies have also provided the understanding that Ca^{2+} signaling pathways are indispensable for intercellular communications that regulate vascular

contractility. Moreover, the individual Ca^{2+} signaling elements can interact with one another to achieve a finer control of vascular function.

There is remarkable heterogeneity in the Ca^{2+} signaling mechanisms among different vascular beds, contributing to functional heterogeneity of SMCs or ECs. The Ca^{2+} signaling elements, their regulatory proteins, and signaling targets vary from large arteries to small arteries and from one vascular bed to another. While the functional effects of most Ca^{2+} signaling pathways are well established at the level of resistance arteries or arterioles, the physiological roles of many pathways at the whole-animal level remain unknown. In some cases, data interpretation is confounded by the presence of an ion channel in both SMCs and ECs. Cell-specific knockout mice will provide a definitive answer to the physiological significance of such pathways in either ECs or SMCs. The Ca^{2+} signaling mechanisms in SMCs and ECs can be activated by mechanical (pressure or flow) or neurohumoral (GPCR signaling, nerve-stimulation) stimuli. Although significant progress has been made in understanding the mechanisms for myogenic vasoconstriction and flow-mediated vasodilation, the precise mechanosensor proteins remain unclear. Recent discoveries suggest that TRPP1, TRPML1, and PIEZO1 channels may represent new Ca^{2+} signaling pathways contributing to mechanosensation in the vasculature. It is anticipated that future studies will reveal newer Ca^{2+} signaling elements, their physiological roles, and abnormalities in pathological conditions. Ca^{2+} signaling mechanisms and signaling organizations of cells have been shown to be abnormal in vascular disorders. Therefore, a major objective of future studies will be to identify “targetable” abnormalities in Ca^{2+} signaling mechanisms in vascular disorders.

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Didactic Synopsis

Major Teaching Points

- Contractile state of small arteries and arterioles determines vascular resistance.
- Vasoconstriction increases vascular resistance and blood pressure, whereas vasodilation reduces vascular resistance and blood pressure.
- Two main cell types in the vascular wall control the contractile state of the small arteries and arterioles: smooth muscle cells (SMC) and endothelial cells (EC).
- Intracellular Ca^{2+} in SMCs and ECs is a crucial controller of vascular contractility.
- Increase in SMC Ca^{2+} mostly causes vasoconstriction, whereas increase in EC Ca^{2+} results in vasodilation.
- Increase in intracellular Ca^{2+} in SMCs and ECs occurs via the influx of extracellular Ca^{2+} or release of Ca^{2+} from intracellular stores.
- Physiological Ca^{2+} signals in SMCs and ECs have unique spatiotemporal properties that enable the activation of specific targets and limit Ca^{2+} toxicity.
- Abnormal Ca^{2+} signaling mechanisms in SMCs and EC contribute to pathogenesis of vascular disorders.

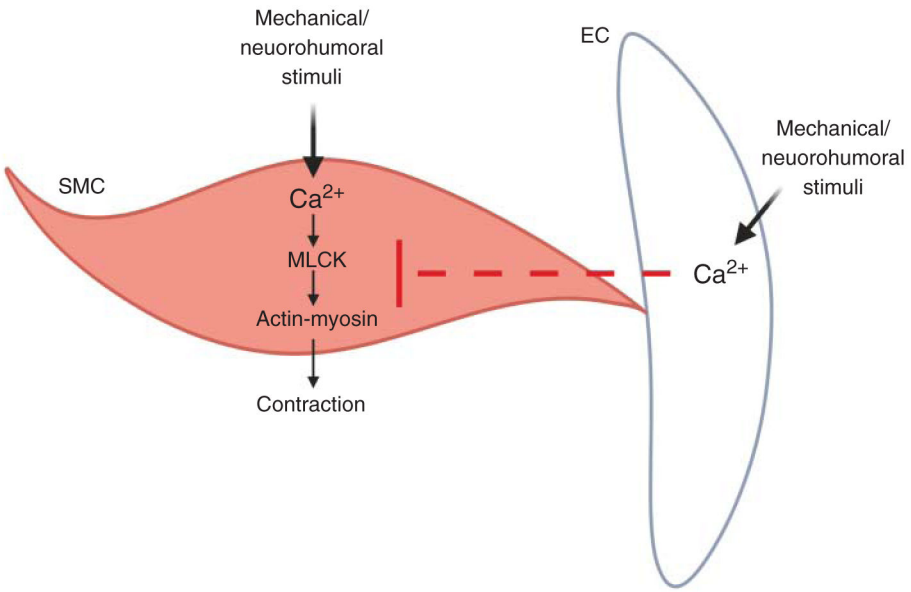

Figure 1. The contrasting effects of smooth muscle cell (SMC) and endothelial cell (EC) Ca^{2+} on vascular contractility.

Mechanical and neurohumoral stimuli can increase intracellular Ca^{2+} in SMCs and ECs. Intracellular Ca^{2+} in SMCs and ECs, in general, has opposite effects on vascular resistance. Increase in SMC Ca^{2+} activates the contractile machinery in SMCs (myosin light chain kinase or MLCK/Actin-Myosin). In contrast, an increase in EC Ca^{2+} inhibits SMC contractile mechanisms. The dotted red line indicates inhibition of SMC contractility.

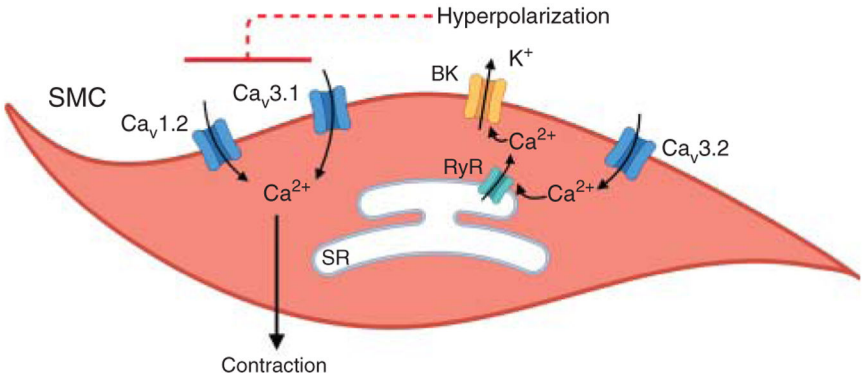

Figure 2. Regulation of vascular smooth muscle cell (SMC) contractility by voltage-gated Ca^{2+} channels.

Ca^{2+} entry through $Ca_V1.2$ and $Ca_V3.1$ channels promotes SMC contraction. Ca^{2+} influx through $Ca_V3.2$ channels activates ryanodine receptors (RyRs), triggering Ca^{2+} release from the sarcoplasmic reticulum (SR) in the vicinity of large conductance, Ca^{2+}-activated K^+ (BK) channels. BK channel activation results in SMC hyperpolarization and vasodilation. The dotted line indicates the deactivation of $Ca_V1.2$ and $Ca_V3.1$ channels.

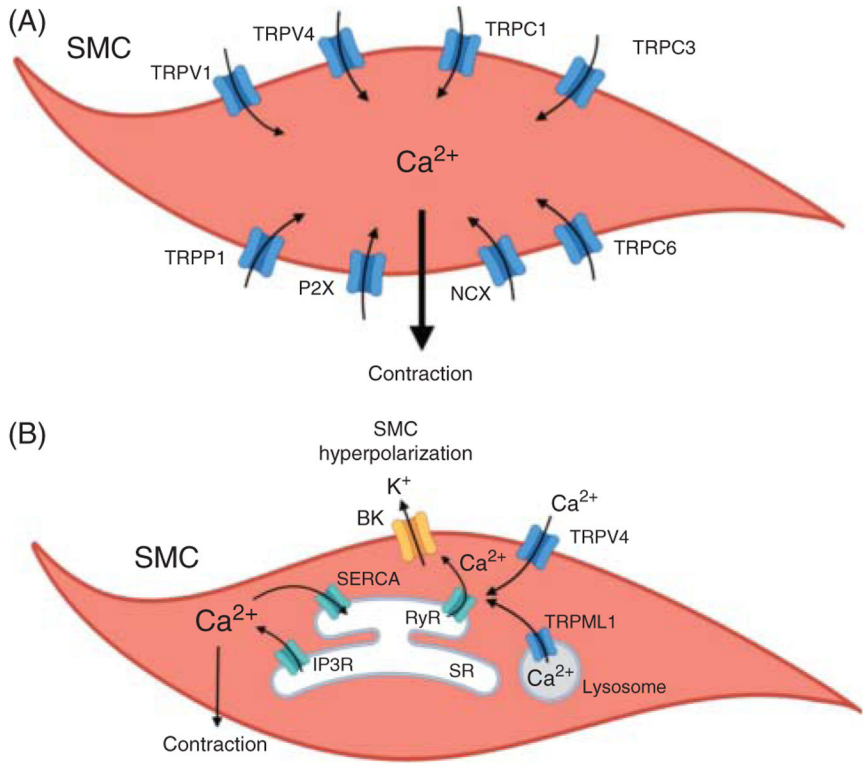

Figure 3. Regulation of vascular smooth muscle cell (SMC) contractility by non-voltage-gated Ca^{2+} entry mechanisms.

(A) Activation of purinergic P2X receptor, TRPV4, TRPV1, TRPP1, TRPC3, and TRPC6 channels, and NCX in reverse mode increases SMC intracellular Ca^{2+}, leading to vasoconstriction. (B) Ca^{2+} release from endolysosome via TRPML1 channel, or Ca^{2+} entry through TRPV4 channel at the plasma membrane activates ryanodine receptors (RyRs), triggering Ca^{2+} release signals (Ca^{2+} sparks) from the sarcoplasmic reticulum (SR). Ca^{2+} sparks activate large-conductance Ca^{2+}-activated potassium (BK) channels. BK channels hyperpolarize the SMC membrane and cause vasodilation. Ca^{2+} release through IP3R induces SMC contraction. Sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA), by sequestering cytoplasmic Ca^{2+} back into the SR, maintains low cytosolic Ca^{2+} concentration. TRPV, TRPP, TRPC, TRPML, members of transient receptor potential channel family; NCX, Na^{+}/Ca^{2+} exchanger.

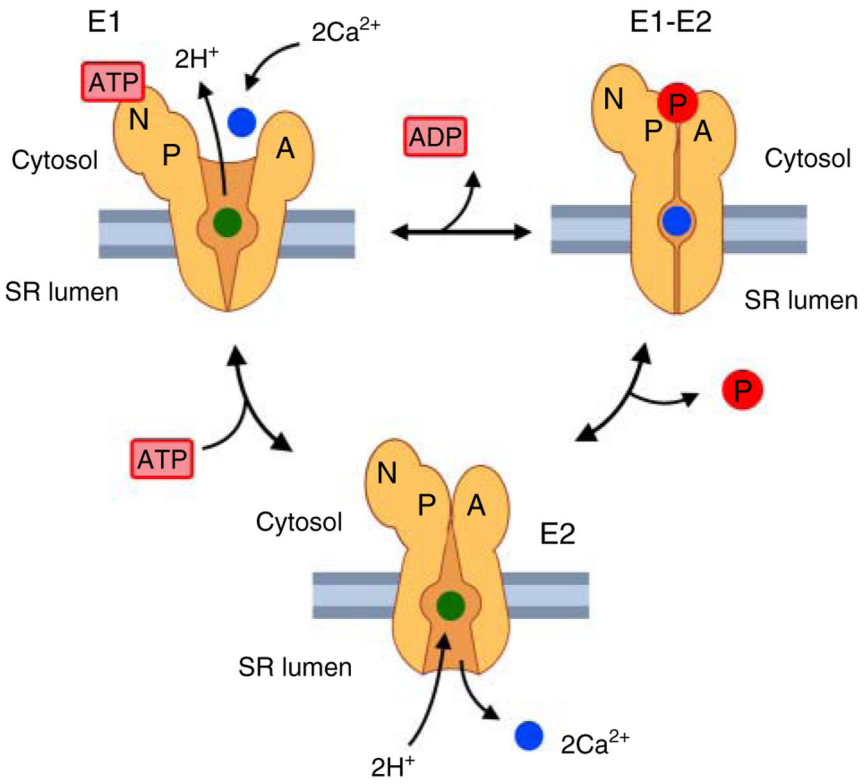

Figure 4. Sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA) transporting cycle.

E1 indicates SERCA conformation characterized by a high affinity for Ca^{2+}. E1-E2 represents a transient high energy state. E2 represents SERCA conformation characterized by a low affinity for Ca^{2+}. Two cytosolic Ca^{2+} ions bind to SERCA in E1 conformation. ATP tethers to the nucleotide (N) domain and phosphorylates the (P) domain. The phosphorylated (P) domain interacts with the (A) domain resulting in two sequential conformational changes (E1-E2, and E2). SERCA in E2 conformation releases Ca^{2+} into the SR lumen. Pi, inorganic phosphate; ADP, adenosine diphosphate; H^+, proton.

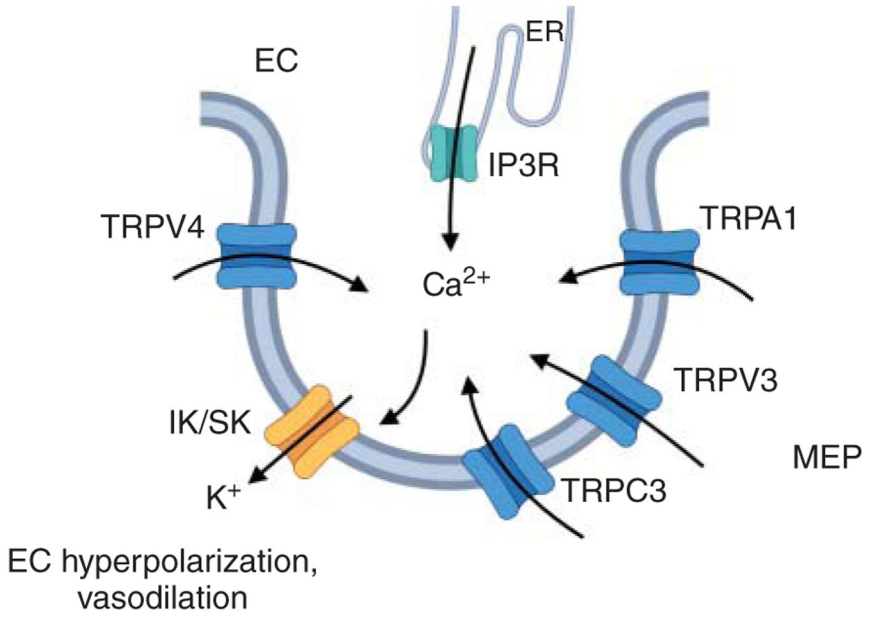

Figure 5. Ca^{2+} signaling networks at myoendothelial projections (MEPs).

Ca^{2+} influx via TRPV4/TRPV3/TRPA1/TRPC3 channels or Ca^{2+} release from the ER via IP3Rs at MEPs activates nearby small (SK) and intermediate (IK) conductance Ca^{2+}-activated K^+ channels. IK/SK channel activation hyperpolarizes endothelial cells (EC) membrane and results in vasodilation. TRPV/TRPA/TRPC, members of transient receptor potential channel family.

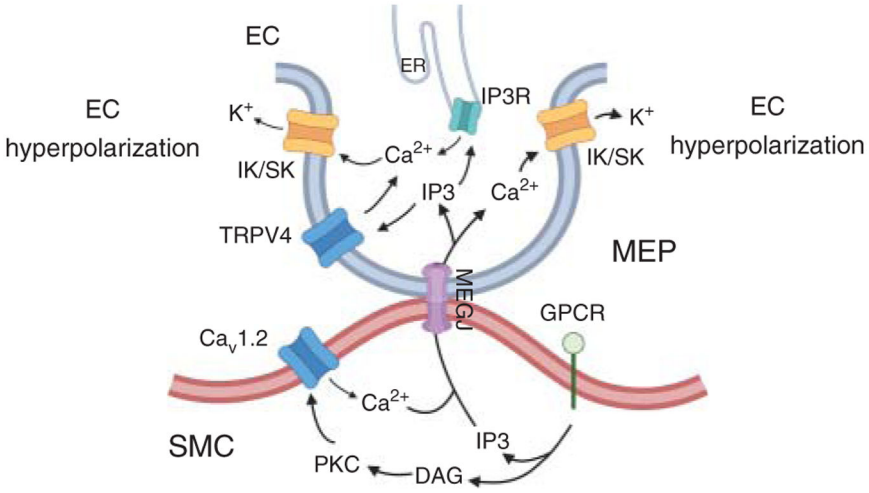

Figure 6. Signaling mechanisms at myoendothelial projections (MEPs) that control the communication between endothelial cells (ECs) and smooth muscle cells (SMCs) and SMC contractility.

Stimulation of Gq-protein coupled receptors (GqPCRs) on SMC membrane leads to the formation of inositol triphosphate (IP3) and diacylglycerol (DAG). DAG activates protein kinase C (PKC), which phosphorylates voltage-gated Ca^{2+} ($Ca_V1.2$) channel, leading to an increase in SMC Ca^{2+} and vasoconstriction. IP3 and Ca^{2+} can diffuse to ECs through myoendothelial gap junctions (MEGJ). Elevation of IP3 and Ca^{2+} at MEPs limits vasoconstriction by activating TRPV4-IK/SK channel and IP3R-IK/SK channel signaling. TRPV4, transient receptor potential vanilloid channel 4 (TRPV4); SK and IK, small (SK) and intermediate (IK) conductance Ca^{2+}-activated K^+ channels.

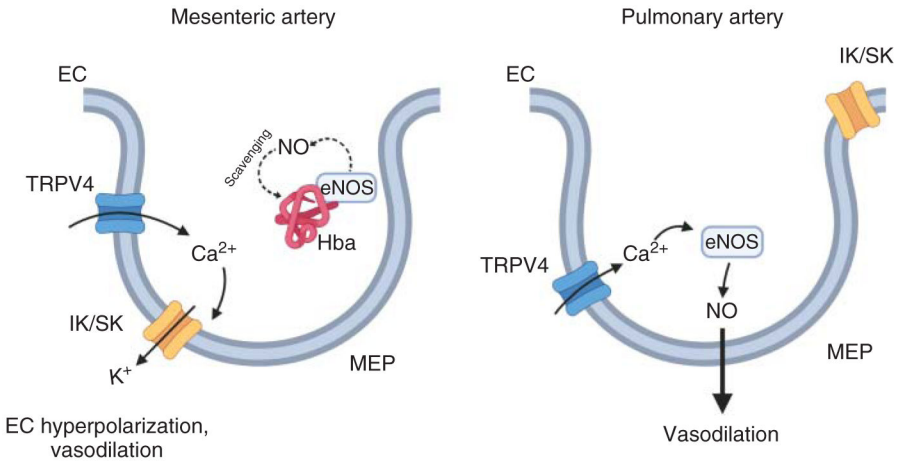

Figure 7. The molecular mechanism underlying selective activation of IK/SK channels in mesenteric arteries versus eNOS in pulmonary arteries.

In mesenteric arteries, Ca^{2+} entry through the TRPV4 channel at the myoendothelial projections (MEPs) determines vasodilation via activation of nearby small (SK) and intermediate (IK) conductance Ca^{2+}-activated K^+ channels. Co-localization of endothelial nitric oxide synthase (eNOS) with hemoglobin alpha (Hbα), a nitric oxide (NO) scavenging protein, prevents TRPV4-eNOS signaling. On the contrary, in pulmonary arteries, IK/SK channels and Hbα do not localize at MEPs. Therefore, Ca^{2+} influx via TRPV4 channel activates eNOS causing NO-dependent vasodilation. EC, endothelial cell.

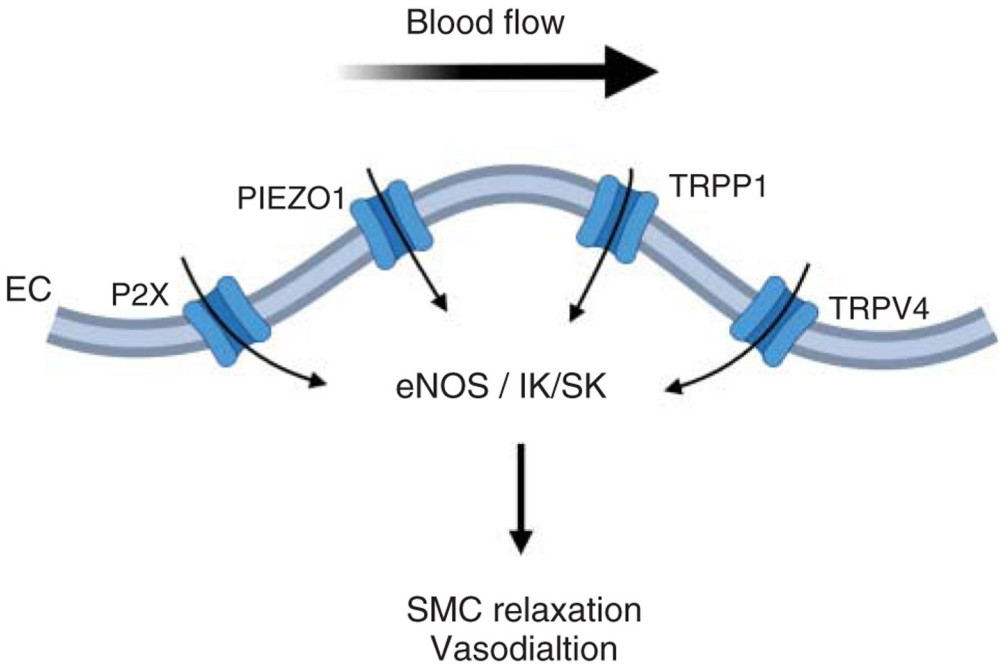

Figure 8. The contribution of endothelial P2X purinergic receptor, PIEZO1, TRPP1, and TRPV4 channels to flow-induced vasodilation.

Sheer stress-dependent activation of P2X, PIEZO1, TRPP1, and TRPV4 channels increases endothelial Ca^{2+}. Shear stress-induced increase in endothelial Ca^{2+} can cause vasodilation via one of the two pathways (i) activation of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO)-mediated vasodilation; and (ii) activation of IK/SK channels, leading to endothelium-dependent hyperpolarization and vasodilation. TRPP1, transient receptor potential polycystic 1 channel; TRPV4, transient receptor potential vanilloid 4 channel.

Table 1

Individual Ca^{2+} Signals in smooth muscle cells (SMCs) and endothelial cells (ECs)

Type of Ca^{2+} signal	Source	Physiological effect	References
VDCC Ca^{2+} sparklets (SMC)	Unitary Ca^{2+} influx events occurring through single VDCCs	• Local and global increases in intracellular Ca^{2+} that cause vasoconstriction (LTCC, TTCC) or vasodilation (TTCC) • Indirect refilling of SR Ca^{2+} stores • NFATc activation influencing gene expression	(16, 314-317, 323, 324, 464)
TRPV4 sparklets (SMC, and EC)	Unitary Ca^{2+} influx events occurring through single TRPV4 channels	• Increase of RyR-BK channels coupling counteracting vasoconstriction (SMC) • Activation of IK/SK channels, hyperpolarization, vasodilation (EC) • Activation of eNOS, vasodilation via NO-cGMP-PKG pathway (EC) • Activation of IP3Rs, formation of Ca^{2+} waves, vasodilation (EC)	(166, 178, 282, 292, 342, 432, 433, 459)
Ca^{2+} sparks (SMC)	Unitary Ca^{2+} release events occurring through RyRs	• BK channels activation, SMC hyperpolarization and vasodilation	(226, 318, 353)
Ca^{2+} blips, puff, and waves (SMC, and EC)	Local (blips and puff) or whole cell propagating (waves) Ca^{2+} release events occurring through IP3Rs	• Ca^{2+} CaM dependent vasoconstriction (SMC) • Activation of IK/SK channels and eNOS, vasodilation (Ca^{2+} waves, EC)	(44, 109, 137, 202, 212, 287, 468)
Ca^{2+} pulsars and wavelets (EC)	Local Ca^{2+} release events occurring at MEPs via IP3Rs	• Activation of IK channels, vasodilation (Ca^{2+} pulsars) • Negative feedback modulation of α1 AR-induced vasoconstriction (Ca^{2+} wavelets)	(242, 488)
JCaTs (SMC)	Local Ca^{2+} influx events occurring through P2X1R activated by ATP release from perivascular nerves	• Ca^{2+}-CaM dependent vasoconstriction	(238, 239, 369)
TRPA1 sparklets (EC)	Unitary Ca^{2+} influx events occurring through TRPA1 channels	• Activation of IK channels, vasodilation	(359, 448)
TRPV3 sparklets (EC)	Unitary Ca^{2+} influx events occurring through TRPV3 channels	• Activation of IK channels, vasodilation	(99, 360)