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Smooth Muscle Ion Channels and Regulation of Vascular Tone in Resistance Arteries and Arterioles

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Abstract

Vascular tone of resistance arteries and arterioles determines peripheral vascular resistance, contributing to the regulation of blood pressure and blood flow to, and within the body's tissues and organs. Ion channels in the plasma membrane and endoplasmic reticulum of vascular smooth muscle cells (SMCs) in these blood vessels importantly contribute to the regulation of intracellular Ca^{2+} concentration, the primary determinant of SMC contractile activity and vascular tone. Ion channels provide the main source of activator Ca^{2+} that determines vascular tone, and strongly contribute to setting and regulating membrane potential, which, in turn, regulates the open-state-probability of voltage gated Ca^{2+} channels (VGCCs), the primary source of Ca^{2+} in resistance artery and arteriolar SMCs. Ion channel function is also modulated by vasoconstrictors and vasodilators, contributing to all aspects of the regulation of vascular tone. This review will focus on the physiology of VGCCs, voltage-gated K^+ (K_V) channels, large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels, strong-inward-rectifier K^+ (K_{IR}) channels, ATP-sensitive K^+ (K_{ATP}) channels, ryanodine receptors (RyRs), inositol 1,4,5-trisphosphate receptors (IP_3Rs), and a variety of transient receptor potential (TRP) channels that contribute to pressure-induced myogenic tone in resistance arteries and arterioles, the modulation of the function of these ion channels by vasoconstrictors and vasodilators, their role in the functional regulation of tissue blood flow and their dysfunction in diseases such as hypertension, obesity, and diabetes.

Introduction

Resistance arteries and arterioles importantly contribute to cardiovascular and whole-body homeostasis by serving as the primary location of vascular resistance that contributes to blood pressure regulation and the distribution of cardiac output among and within the body's organs and tissues to meet their metabolic and physiological demands (316). Vascular smooth muscle cells (SMCs) that make up the wall of resistance arteries and arterioles serve as the primary effectors in the minute-to-minute, active regulation of vascular resistance via modulation of the steady-state contraction of these cells, or vascular tone (316). Vascular

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tone of resistance arteries and arterioles depends on the blood pressure within these vessels, as well as the balance between vasoconstrictor and vasodilator signals that impinge upon them (316). Blood pressure, by stretching the SMCs, activates signaling pathways to produce myogenic tone, a hallmark of resistance arteries and arterioles (299, 314, 315, 488, 595, 1036). Myogenic tone serves as the baseline SMC contraction upon which vasoconstrictor and vasodilator signals from neurotransmitters, hormones, endothelium-derived substances, local metabolites and ions act (316). Intracellular Ca^{2+} in SMCs serves as a key determinant of vascular tone by controlling the activity of myosin-light-chain kinase and the degree of phosphorylation of the 20-kD myosin light chains (748). Ion channels in both the plasma membrane and endoplasmic reticulum (ER) serve as the primary sources of activator Ca^{2+} (152, 555, 748, 835). Plasma membrane ion channels also importantly contribute to setting and modulating membrane potential, which not only determines the magnitude of Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCCs), but also, in part, sets the electrochemical gradient for the movement of ions through all plasmalemmal ion channels (666). Membrane potential also impacts the release of Ca^{2+} from intracellular stores and the Ca^{2+} sensitivity of the contractile machinery in vascular SMCs (327, 419, 420, 459, 798, 895, 930, 1105, 1448, 1571, 1574, 1580). Therefore, ion channels importantly contribute to all aspects of the determination and modulation of vascular tone in resistance arteries and arterioles.

Resistance artery and arteriolar SMCs express a plethora of ion channels including, but not limited to: two or more classes of VGCCs (Table 1, Fig. 1), four or more classes of K^+ channels (Table 2, Fig. 1), two or more intracellular Ca^{2+} release channels (Table 3, Fig. 1), multiple members of five classes from the transient receptor potential (TRP) family of ion channels (Table 4, Fig. 1), two or more classes of Cl^- channels (184, 303, 304, 584, 632, 829, 956, 957) and members of the epithelial Na^+/acid-sensing channel (ENaC) (340–342, 460, 502, 510, 698, 697, 1465). This review will focus on VGCCs, K^+ channels, ER Ca^{2+} release channels and TRP channels that contribute to myogenic and agonist-modulated tone in vascular SMCs of resistance arteries and arterioles. Chloride channels (184, 303, 304, 584, 632, 829, 956, 957) and ENaC (340–342, 460, 502, 510, 698, 697, 1465) that may contribute to myogenic- and agonist-induced tone of some resistance arteries and arterioles will not be discussed. Ion channel function in the pulmonary circulation also will not be reviewed in detail (937). We will focus on ion channel function in establishing myogenic tone in resistance arteries and arterioles, the role played by these channels in the mechanism of action of vasodilators and vasoconstrictors that modulate vascular tone and the effects of disease states such as hypertension, obesity, and diabetes on ion channel expression and function. The relationships between these diseases and SMC ion channel expression and function are complex and multifaceted: changes may directly contribute to disease progression, changes may result from disease progression, or changes may be a means of compensation to account for the pathophysiological progression of a disease. Where possible, this review presents the relationship between SMC ion channels and disease from these different perspectives.

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Approaches Used to Study Ion Channels in Resistance Arteries and Arterioles

The study of ion channel expression and function in SMCs of resistance arteries and arterioles requires the application of multiple methods applied to preparations that range from patch-clamp of freshly isolated SMCs, to pressure myography of isolated vessels, to *in vivo* imaging of arterioles in the living microcirculation of anesthetized animals, to the measurement of blood flow and blood pressure in conscious, freely moving animals. While cultured cells can be utilized for patch-clamp study of the biophysical properties of ion channels and the potential for their modulation by interactions with other proteins and post-transcriptional modification, this approach is not viable for the study of the physiological function of a given channel due to the ion channel remodeling that occurs as cells proliferate in culture (103, 625, 1037, 1425, 1443). Patch-clamp (102, 105, 106, 110, 154, 175, 308, 458, 646, 672, 673, 1072, 1075, 1544) and imaging (41, 266, 994, 1061, 1071) approaches applied to SMCs freshly isolated from resistance arteries or arterioles (114, 673, 1072, 1075, 1186) are required to define the functional expression and activity of an ion channel in its native context. However, it should be understood that this approach also is limited because isolated cells are usually studied at room temperature and are not exposed to the signaling environment (pressure-induced cell strain, exposure to hormones and neurotransmitters, signaling generated from interactions with the extracellular matrix, homotypic and heterotypic interactions with other cells, etc.) that occurs in the native environment of the vessels.

Isolated resistance arteries and arterioles studied by pressure myography (349, 542) provide additional information about the physiological function of an ion channel in a more complete system where the SMCs are exposed to physiological temperature, pressure-induced stress and strain, interactions with the extracellular matrix and interactions with other cells. In this setting, the use of microelectrodes to monitor membrane potential (185, 380, 763), imaging approaches to visualize global and local Ca^{2+} signals (393, 683, 764, 1527, 1528), the measurement of diameter to assess SMC contractile function, the judicious use of channel blockers and the use of genetically modified animal models provides an integrated view of ion channel function in these important vessels. However, it is not yet possible to apply patch-clamp methods to SMCs in this native environment in pressurized vessels because these cells are embedded in extracellular matrix proteins. Hence, the ion channel “signature” information (single channel conductance, channel kinetics, current-voltage relationship, etc.) that can be resolved by patch-clamp is not yet available with the study of intact vessels. Therefore, the ability to resolve the function of a single class of ion channels in pressure myography experiments is limited to the selectivity of available blockers (which is often lacking) and/or the availability of genetically modified animal models. In addition, isolated vessels are not tethered to the extracellular matrix as they are, *in vivo*, and neural and hormonal input are absent. Isolated vessels also lack input from upstream and downstream segments of the microvascular network from which they were removed. Furthermore, pressure myography is limited by our ability to dissect vessels with sufficient unbranched length to be cannulated, and have an anatomical location that is amenable to surgical isolation of the vessels; hence not all vessels can be studied.

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The study of resistance arteries and arterioles by intravital microscopy (79, 147, 244, 348, 587, 847, 1276, 1524, 1603) allows interrogation of vessels in their native environment, removing some of the shortcomings of the study of isolated vessels while adding additional limitations that include lack of control of the environment (blood pressure, blood flow, hormonal and neural input, etc.) and difficulty identifying the cellular site of action of ion channel blockers, which are necessary to define the role of a specific ion channel in a physiological process. The use of cell-specific, conditional knockout animal models coupled with careful pharmacology can help resolve some of these issues. However, the necessary use of anesthetics adds additional constraints on interpretation of data from intravital experiments. Approaches to visualize resistance arteries and arterioles in conscious animals, in the absence of anesthetics have been developed, but are limited in their application (393, 586, 1093).

The measurement of blood pressure (1253) and blood flow (463, 516, 812, 1159, 1368) in intact animals provides a 30, 000 ft view of the integrated function of resistance artery and arteriolar networks. However, these approaches do not provide the resolution to define the site of action of drugs or interventions on ion channel function that can be achieved by the study of single cells or isolated vessels, *in vitro*, or imaging of single vessels or microvascular networks, *in vivo*.

Thus, all of the approaches available to study ion channel function in resistance arteries and arterioles have unique limitations that should be acknowledged. Only when combined do they provide a complete view of the function of a given SMC ion channel in the physiology and pathophysiology of these vessels.

Voltage-Gated Ca^{2+} Channels

VGCCs transduce membrane depolarization into augmented Ca^{2+} influx into vascular SMCs and play an important role in the regulation of both contraction and gene expression in vascular SMCs (316, 599, 600, 1026, 1073). They are members of a gene superfamily of plasma membrane ion channels that includes voltage-gated Na^+ channels and voltage-gated K^+ channels (210).

Discovery of VGCCs

Calcium-based action potentials, the first evidence for VGCCs, were recorded from crustacean muscle by Fatt and Katz (412). Later, currents through Ca^{2+}-selective channels were recorded in cardiac Purkinje fibers (1200) and it subsequently became apparent that there were multiple classes of VGCCs (101, 208). The original characterization of VGCCs was based on the pharmacology and electrophysiological characteristics of currents through these channels (101, 208). L-type Ca^{2+} currents activated at relatively positive potentials (high voltage of activation: threshold at −30 to −40 mV), had high single channel conductances (20–27 pS with 110 mmol/L Ba^{2+} as the charge carrier), showed slow voltage-dependent inactivation, displayed long lasting currents with Ba^{2+} as the charge carrier, and were inhibited by dihydropyridine, phenylalkylamine, and benzothiazepine organic Ca^{2+} channel blockers (101, 208, 1433). T-type Ca^{2+} currents activated at relatively negative membrane potentials (−60 to −70 mV), showed rapid voltage-dependent inactivation, had

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small single channel conductances (8 pS in 110 mmol/L Ba^{2+}), and were relatively insensitive to organic Ca^{2+} channel blockers (101, 208, 1433). Currents through some neuronal Ca^{2+} channels appeared to be intermediate between L- and T-type and could be distinguished by their sensitivity to ω-conotoxin and were categorized as N-type currents (101, 208, 1433). P-type Ca^{2+} currents were later identified in Purkinje neurons and were recognized by their sensitivity to blockade by ω-agitoxin, but not organic Ca^{2+} channel blockers or ω-conotoxin (101, 208). Q-type Ca^{2+} currents have similar characteristics to P-type, but show lower sensitivity to block by ω-agitoxin (208). Finally, R-type Ca^{2+} currents were identified that were high-voltage-activated, but resistant to organic Ca^{2+} channel blockers and the toxins that block N-, P-, and Q-type currents (208).

Ten distinct genes are now recognized, divided into three main subfamilies that encode the pore-forming α_1 subunits of VGCCs (210): Ca_V 1, Ca_V 2, and Ca_V 3 (210). The Ca_V 1 subfamily contains four members (Ca_V 1.1, 1.2, 1.3, and 1.4) that represent channels that carry high-voltage-activated, long lasting (L)-type Ca^{2+} currents. The Ca_V 2 subfamily (Ca_V 2.1, 2.2, and 2.3) includes channels that carry P/Q-, N-, and R-type currents, respectively. The Ca_V 3 family members (Ca_V 3.1, 3.2, and 3.3) constitute low-voltage-activated, transient (T)-type VGCCs.

Alternative splicing amplifies the number of gene products from the ten genes encoding these channels. For example, splice variants of Ca_V 1.2 in domain I, segment 6 distinguish L-type Ca^{2+} channels expressed in the heart (Ca_V 1.2a) from those in vascular SMC (Ca_V 1.2b), and account for differences in the pharmacology and biophysics of L-type Ca^{2+} channels expressed in these tissues (1515).

Structure of VGCCs

VGCCs consist of a large, ~190 kD α_1 subunit, that forms the ion-conducting pore and contains the voltage sensors, gating apparatus and sites of channel regulation by drugs, second messengers and toxins (209, 210). There is a common theme regarding the structure of the pore-forming portion of all of the ion channels covered in this review, as depicted in Figure 2. Two membrane spanning domains (either alone as for K_{IR} channels, or as part of 6-transmembrane domain structures) and a connecting pore-forming loop (P-Loop) contribute to the channels' pores, with four such units coalescing to form the ion conducting portion of the channels. Modulatory β, α_2, and δ subunits are present in most types of VGCCs, with γ subunits also found in channels expressed in skeletal muscle and parts of the brain (209, 210). The β and $\alpha_2\delta$ subunits are important for expression of the channels in the plasma membrane (209). These accessory subunits also modulate the voltage dependence and the gating kinetics of VGCCs (209). There are four genes that encode the β-subunits ($\beta_{1–4}$) and four that encode the $\alpha_2\delta$ subunits ($\alpha_2\delta_{1–4}$) (195, 209). Both are also subject to alternative splicing (195, 209). Vascular SMCs express β_2 (283), β_3 (745, 1038, 1039), $\alpha_2\delta_1$ (87, 88, 283) and $\alpha_2\delta_3$ (283) isoforms of these accessory subunits.

The α_1 subunit of VGCCs consists of four sets (I–IV) of six transmembrane spanning domains (S1–S6) linked by intracellular peptide loops (208, 209), similar to the structure of voltage-gated sodium channels (207, 209). The pore of the channel is formed by segment 6 and the peptide loop (P-loops) between segments 5 and 6 of the four domains (Fig. 2), and

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the voltage sensor is located in the S4 segments (208, 209). Glutamate residues in the P-loops form the selectivity filter and residues in segment 6 form the binding site for organic Ca^{2+} channel blockers (209). The N- and C-terminal domains are both intracellular (209). Accessory β subunits are located intracellularly and bind to the α-interaction domain in the intracellular P-loop between domains I and II (209). The α_2 subunit is located extracellularly and is linked to the δ subunit by a disulfide bridge (209). The δ subunits are postranscriptionally modified with a glycophosphatidylinositol membrane anchor, tethering these proteins to the membrane in association with the α_1-pore-forming subunit (209). Cerebrovascular SMCs express $\alpha_2\delta_1$ subunits that are essential for trafficking and targeting Ca_V 1.2 VGCCs to the plasma membrane (87, 88). Vascular SMCs also express β2 (283) and/or β3 subunits (745) that increase the stability of the channel proteins by inhibiting their degradation, and which mediate upregulation of the channels by angiotensin II.

Calcium channels exist in signaling complexes with a large number of binding partners that contribute to the localization and regulation of these VGCCs (195, 302, 565, 1064, 1442). For example, in addition to the β_3, and $\alpha_2\delta_1$ subunits, Ca_V 1.2 in vascular SMCs also associates with the scaffolding protein, A-kinase anchoring protein (AKAP) 150, which targets protein kinase C (PKC) (1063), protein kinase A (PKA) (1065), and the protein phosphatase, calcineurin (PP2b) (1064) to the channel and is required for kinase-dependent regulation of the Ca_V 1.2 (see following text for more on this topic). The C-terminus of Ca_V 1.2 also binds calmodulin, which contributes to both Ca^{2+}-dependent inactivation and facilitation of Ca_V 1.2 (1458, 1658). Based on studies in other systems, such as the heart (565) and neurons (195) additional binding partners are likely.

Evidence for VGCCs in vascular SMCs

Early evidence for the presence of VGCCs in vascular SMCs came from studies demonstrating inhibition of vascular SMC contraction (429, 482, 1147) and block of vascular SMC Ca^{2+}-dependent action potentials (108, 554) by organic VGCC blockers (Table 1). Subsequently, application of patch clamp approaches identified voltage-gated, Ca^{2+}-selective single channel currents in membrane patches from vascular SMCs isolated from rabbit mesenteric arteries that were potently inhibited by the VGCC blocker, nisoldipine and activated by the dihydropyridine Ca^{2+} channel agonist, BayK 8644 (1544). Two populations of single channel events were detected in these experiments with conductances of 8 and 15 pS (in 80 mmol/L Ba^{2+}) suggesting the expression of two classes of VGCCs. Whole-cell recordings of macroscopic Ca^{2+} currents from vascular SMCs from rat mesenteric arteries also identified two separable Ca^{2+} currents (102): a fast-inactivating current with activation threshold at −40 mV and a slowly inactivating current with threshold activation at −10 mV with 115 mmol/L Ba^{2+} as the charge carrier. The slowly inactivating current displayed voltage-dependent block by nitrendipine and activation by Bay K 8644, whereas the fast-inactivating current was resistant to block by nitrendipine. The voltage dependence, kinetics and pharmacology of the currents reported by Bean et al. (102) were very similar to those reported in cardiac myocytes (100), and were the first to provide evidence for the presence of both L-type and T-type VGCCs in vascular SMCs. Similar results were reported in SMCs isolated from rat Azygos vein (1349). Currents resembling

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those through L-type and T-type channels were also reported in vascular SMCs isolated from rabbit ear artery at both the whole-cell and single channel levels (113).

Pharmacology of vascular SMC VGCCs

VGCCs display distinct pharmacology that can help in the identification of the specific channels that function in systems where multiple VGCCs are expressed (Table 1). Dihydropiridines such as nifedipine and nimodipine are relatively selective blockers of Ca_V 1.2 channels expressed in vascular SMCs, (Table 1). The phenylalkylamine, verapamil, and the benzothiazepine, diltiazem are likewise relatively selective blockers for this class of VGCCs (Table 1) and can allow separation of processes mediated by Ca_V 1.2 and Ca_V 3 channels, for example. However, as with all drugs, care must be taken with the concentrations used. For example, nifedipine at nanomolar concentrations (IC_{50} = 10–100 nmol/L) (872) and diltiazem at low micromolar concentrations (IC_{50} = 500 nmol/L) (615) are quite selective for Ca_V 1.2 channels. However, both of these drugs also block some voltage-gated K^+ channels at higher concentrations: for example, the IC_{50} for K_V 1.2 is 20 μmol/L for nifedipine and 200 μmol/L for diltiazem (504). This is not a problem in patch clamp studies where the voltage and ionic characteristics of currents can be isolated. However, in studies of isolated vessels and especially *in vivo*, where a number of channels are functioning simultaneously, the typical use of high concentrations of these drugs to ensure channel blockade also insures the likelihood of off-target effects.

Dihydropyridine blockers and activators of Ca_V 1.2 channels display significant voltage dependence: they are more effective at depolarized membrane potentials, and bind preferentially to the inactivated state of the channels (1252). Thus, translation of IC_{50} or EC_{50} data for these compounds from typical patch clamp experiments, where SMCs are held at very negative membrane potentials (e.g., −80 mV), to experiments in pressurized vessels that develop myogenic tone in which SMCs are relatively depolarized (e.g., −30 to −40 mV), is difficult. This likely explains the potent activation of L-type VGCCs by Bay K 8644 (EC_{50} = 6 nmol/L) reported by Zheng et al. (1638) for contraction of vascular smooth muscle, relative to patch clamp reports for cardiac myocytes (EC_{50} = 30 nmol/L) (546).

The divalent metal ions, Cd^{2+} and Ni^{2+} also display some selectivity for classes of VGCCs expressed in vascular SMCs (Table 1). For Cd^{2+}, Ca_V 1.2 channels (IC_{50} = 7 μmol/L) (1054) are blocked at lower concentrations than are Ca_V 3.1 and 3.2 channels (IC_{50} = 160 μmol/L) (833). Nickel ions can be used to separate currents through Ca_V 3.2 channels (IC_{50} = 5.7–12 μmol/L) (833) from currents through Ca_V 1.2 (IC_{50} = 280 μmol/L) (1054) and Ca_V 3.1 (IC_{50} = 167–250 μmol/L) (833) channels. However, Cd^{2+} also blocks the Na^+/Ca^{2+} exchanger with an IC_{50} = 321 μmol/L such that off target effects are likely at concentrations of Cd^{2+} of 100 μmol/L or greater (605).

Selective blockade of Ca_V 3, T-type channels can be achieved with kurtoxin, which is quite selective for these channels, relative to Ca_V 1.2 channels (Table 1). Mibefradil, on the other hand, is not as selective (Table 1), making its use in intact tissue and *in vivo*, problematic. Newer, small molecule blockers of Ca_V 3 channels, such as ML 218 (1560) may prove useful. However, the use of this compound in vascular systems has not been reported.

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L-type VGCCs and myogenic tone

The early studies outlined earlier provided the first evidence that vascular SMCs express multiple classes of VGCCs. Importantly, they demonstrated that the inhibitory effects of dihydropyridine Ca^{2+} channel blockers on SMC tone (429) were consistent with effects of this class of VGCC blocker on L-type channels which appear to provide a major source of activator Ca^{2+} in vascular SMCs in the wall of resistance arteries (1073). This has been confirmed in rat middle cerebral arteries where the voltage dependence of intracellular Ca^{2+} and myogenic tone matches that for currents through L-type VGCCs, and both depolarization-induced increases in intracellular Ca^{2+} and myogenic tone are prevented or reversed by the L-type VGCC blockers nisoldipine and diltiazem (764). These SMCs express a splice variant of Ca_V 1.2 in exon 1 that alters the effects of $\alpha_2\delta_1$ and β_3 VGCC subunits on the membrane insertion and protein stability of these channels and produces a leftward (negative) shift in the voltage-dependent activation of the channels (236). Additional splice variants have also been identified in these cells (237).

As noted earlier, data from rat cerebral arteries indicate that Ca^{2+} influx through Ca_V 1.2-containing L-type VGCCs is the major source of activator Ca^{2+} involved in pressure-dependent, myogenic tone. This conclusion is supported by studies of skeletal muscle resistance arteries from conditional, SMC-specific knockout of Ca_V 1.2, in which pressure-induced myogenic tone was absent from vessels isolated from the knockouts at pressures above 40 mmHg, and where reduced vascular resistance of perfused hind limb preparations was observed (1026). However, interpretation of these data is complicated by findings that L-type VGCCs are essential for initiation of myogenic tone, but perhaps not all of the steady-state tone of some vessels (785).

Studies of other vessels support a significant, but not exclusive role for Ca^{2+} influx through L-type channels in myogenic tone. In first-order Sprague-Dawley rat cremaster muscle arterioles, the relationship between membrane potential and tone is steeper than observed in cerebral arteries (764), and in these rat cremaster arterioles, only 33% of Ca^{2+}-dependent tone was eliminated by nifedipine (1 μmol/L) (785), suggesting that Ca^{2+} influx through L-type VGCCs is not the sole source of activator Ca^{2+} in this tissue. In contrast, cumulative nifedipine concentration-response studies by this same group indicated that Ca^{2+} influx through L-type VGCCs accounted for >70% of Ca^{2+}-dependent myogenic tone in a subsequent study in the same arterioles (1171). The reason for this difference in the role played by L-type VGCCs between these studies is not apparent. Nonetheless, the former study showed that preincubation of the arterioles with nifedipine (1 μmol/L) prevented the development of pressure-induced myogenic tone indicating an essential role for L-type VGCCs in the initiation phase of the response to increased transmural pressure in cremaster arterioles, consistent with studies in most other vessels (315, 316, 596, 600).

Several *in vivo* studies also support a major role for L-type VGCCs in myogenic tone, at rest. Nifedipine, at concentrations where it selectively blocks L-type VGCCs, produces nonmaximal dilation of pial arterioles in anesthetized cats (169). This dihydropyridine also eliminates norepinephrine-induced myogenic reactivity in first-order rat cremaster arterioles, *in vivo* (885). Diltiazem or verapamil dilated arterioles in rat cremaster muscles, *in vivo* (717). In anesthetized pigs, diltiazem increases blood flow, nonmaximally, at a normal

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perfusion pressure of 100 mmHg and severely impairs blood flow autoregulation (127). Similarly, the L-type VGCC blocker, nicardipine, increases coronary blood flow in the hearts of anesthetized dogs (768). In some instances, nifedipine has been shown to dilate arterioles in the cremaster muscle of anesthetized mice (627, 634, 967) [although contrary results have been reported (1079, 1149)—see later]. Nifedipine also dilates rat epi-neural arterioles *in vivo*, supporting a role for L-type VGCCs in resting myogenic tone in these arterioles (1234).

In distinct contrast, there are a number of studies showing little or no effect of L-type VGCC blockers on resting myogenic tone or blood flow. Hill and Meininger (599) studied rat cremaster arterioles by intravital microscopy. These vessels had substantial myogenic tone (resting diameter was ~50% of maximal diameter), and the hyperpolarizing vasodilator, pinacidil, produced 94% dilation, suggesting that tone in these vessels arose from a voltage-dependent mechanism. However, neither nifedipine nor methoxyverapamil significantly dilated the arterioles at concentrations where they should maximally block L-type VGCCs. The authors did find that the VGCC blockers abolished vasomotion, establishing the efficacy of the drugs in this system. Similar results have been obtained for arterioles in hamster cremaster muscles (670), where nifedipine did not produce steady-state dilation of arterioles with substantial myogenic tone, but abolished vasomotion of these vessels. A lack of effect of nifedipine on resting diameter of cheek pouch arterioles, *in vivo*, was reported by Boric and colleagues (159). Similarly, myogenic tone resistant to L-type VGCC blockade was also reported by Welsh et al. (1522) in the hamster cheek pouch where resting diameters of arterioles were not significantly influenced, in the steady state, by either nifedipine or diltiazem at concentrations that blocked constrictions induced by elevated extracellular K^+ or elevated solution PO_2. As in rat cremaster muscle, arterioles in hamster cremaster and cheek pouch dilate when exposed to K^+ channel agonists such as cromakalim or pinacidil (664) indicating the voltage-dependence of resting tone in these preparations. In the cremaster muscle of anesthetized mice, nifedipine (1079) or diltiazem (1149) had no effect on resting arteriolar tone, in contrast to studies noted earlier (627, 634, 967). Nifedipine also is without effect on resting coronary blood flow in conscious dogs (77) and pigs (126) instrumented for coronary blood flow measurements. The lack of effect of L-type VGCC blockers on resting myogenic tone in these systems suggests that voltage-dependent Ca^{2+} influx pathways other than L-type VGCCs are involved in resting myogenic tone, *in vivo*, whereas the same arterioles studied by pressure myography, *in vitro*, invariably depend heavily on L-type VGCCs. The presence of T-type VGCCs in addition to L-type VGCCs, as reported in rat cremaster arterioles (1460), might provide an explanation, particularly if membrane potential was slightly more hyperpolarized, *in vivo*. While not statistically significant, SMC membrane potential in hamster cheek pouch arterioles has been reported to be slightly more hyperpolarized *in vivo* (−41 ± 4 mV) than what was measured in similar vessels, *in vitro* (−33 ± 1 mV) (670).

L-type VGCCs and vasomotion

Vasomotion, rhythmic oscillations in vessel diameter, is a hallmark characteristic of arterioles in the microcirculation. A number of studies, *in vivo* and *in vitro*, have shown that blockers of L-type VGCCs inhibit vasomotion (1, 93, 522, 523, 529, 599, 670, 998, 1010).

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While there are exceptions to this rule (530), the majority of published studies indicate that vasomotion depends on Ca^{2+} influx through L-type VGCCs.

Vasoconstrictors and L-type VGCCs

With few exceptions, vasoconstrictor agonists that act through $G_{q/11}$-coupled receptors cause contraction of SMCs in blood vessels that can be inhibited, at least in part, by organic L-type VGCC blockers (53, 55, 133, 138, 146, 211, 212, 369, 482, 532, 611, 635, 657, 808, 809, 901, 959, 1007, 1073, 1075, 1138, 1242, 1337, 1367, 1447, 1449, 1545, 1649). This is due to not only agonist-induced depolarization of the SMC membrane, but also to a direct augmentation of the function of L-type VGCCs by the agonists (611). Supporting these pharmacological findings, SMC-specific knockout of Ca_V 1.2 decreases contractions induced by the α_1-adrenoreceptor agonist, phenylephrine, in mouse resistance arteries (1026). Similarly, siRNA knockdown of Ca_V 1.2 in rat mesenteric arteries severely compromises norepinephrine-induced contraction (795).

In SMCs from rabbit ear artery, Benham and Tsien (114) found that norepinephrine increased whole-cell currents through L-type VGCCs. These results were difficult to interpret, however, because the effects of norepinephrine could not be inhibited by phentolamine, prazosin, or propranolol. Nelson et al. (1075) demonstrated that the voltage dependence of contraction induced by norepinephrine in rabbit mesenteric arteries was similar to that for L-type VGCCs and that this adrenergic agonist increased the open-state probability of single L-Type VGCCs independent from changes in membrane potential. As the agonist was applied outside the membrane patch (i.e., in the bath solution), the authors concluded that a second-messenger system must be involved in the adrenoreceptor augmentation of L-type VGCC function. Subsequent studies of SMCs from a number of vascular beds have confirmed these initial reports and extended them to different G-protein coupled receptor agonists including serotonin (5-HT) (1545), histamine (657), angiotensin II (64, 199, 204, 927, 928, 1470, 1477), and endothelin (494, 496, 648, 1304).

The mechanisms by which $G_{q/11}$-coupled receptor agonists increase the open-state probability of VGCCs appears to depend on activation of PKC (740) (Fig. 3). Based on the effects of antagonists of different PKC isoforms, it appears that both conventional (α, β_1, β_2, and γ) and novel (δ, ε, η, and θ) isoforms of PKC can modulate Ca_V 1.2 VGCCs. PKC-α is targeted to Ca_V 1.2 via AKAP150 (1063) and produces persistent opening of Ca_V 1.2 clusters, resulting in high activity Ca_V 1.2-Ca^{2+} sparklets that appear to significantly contribute to global intracellular Ca^{2+} levels in SMCs from murine cerebral and mesenteric arteries (41, 1061, 1063) and myogenic tone (1063). This mechanism may not be functional in all vessels or species as there are several instances in the literature where effective inhibition of PKC does not substantially inhibit nifedipine-sensitive myogenic tone (597, 662, 690). In SMCs from portal vein, activation of α_1-adrenoreceptors coupled via $G_{q/11}$ or α_2-adrenoreceptors coupled to G_i each activate L-type VGCCs via a PKC-dependent pathway (845, 1009). A novel PKC has been proposed to contribute to $G_{q/11}$-coupled receptor-mediated enhancement of current through L-type VGCCs in these same cells (192). In this pathway, the $\beta\gamma$ subunit of the G-protein activates phosphatidylinositol 3,4,5-trisphosphate (PiP_3) Kinase γ ($PiP_3K\gamma$), which, in turn, activates a novel PKC,

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phosphorylating and activating the proto-oncogene tyrosine-protein kinase Src (c-SRC), which then acts on the L-type-VGCCs to increase channel activity (192) (Fig. 3). The role of the PKC-c-SRC pathway in agonist-induced enhancement of L-type VGCC currents and vasoconstriction to other G-protein coupled receptors in other vessels has not been established. However, a role for the $G_{\beta\gamma}$, $PiP_3K\gamma$, and PKC also has been proposed for angiotensin II-induced stimulation of currents through L-type VGCCs (927, 928, 1189, 1478). In contrast, it has been shown that phosphatidylinositol 3,4,5-trisphosphate (PiP_3) produced by $PiP_3K\gamma$ increases the activity of L-type VGCCs directly and accounts for angiotensin II-induced augmentation of Ca^{2+} channel activity independent from PKC (828) (Fig. 3). This may account for angiotensin II signaling via receptors coupled to $G_{12/13}$ and PiP3Kγ (828, 927, 1189, 1478). Chronic stimulation of vascular SMCs with angiotensin II leads to increased expression of L-type VGCCs in the plasma membrane that is mediated by $PiP_3K\gamma$ induced activation of PKB/Akt, phosphorylation of β_{2a} subunits and inhibition of degradation (increased stability) of these channels in other systems (204, 1477).

As noted earlier, c-SRC also appears to modulate the activity of Ca_V 1.2 VGCCs through PKC-dependent (192) and independent mechanisms (515). Like PKC α, c-SRC has been shown to promote persistent activity of Ca_V 1.2 and resulting VGCC-Ca^{2+} sparklets via phosphorylation of a tyrosine residue (Y^{2122}) in the C-terminus of the channel's α subunit (515). c-SRC resides in macromolecular complexes with Ca_V 1.2 and associates with the C terminus (515). Davis and colleagues (221, 513, 515, 1550) demonstrated that fibronectin engagement of $\alpha_5\beta_1$ integrin leads to association of c-SRC and the integrin complex with Ca_V 1.2 and enhancement of currents through the channel (Fig. 3). This has been proposed to be involved in the myogenic response and mechanotransduction by SMCs (315–317, 600). In contrast, engagement of $\alpha_v\beta_3$ integrins reduces currents through Ca_V 1.2 (1552). This latter response may be involved in the vascular response to local injury (1552).

L-type VGCCs and voltage-dependent release of intracellular Ca^{2+}

In some vascular SMCs, membrane depolarization induces release of Ca^{2+} from internal stores (326, 327, 419, 1448). In this pathway it has been proposed that membrane depolarization is sensed by the VGCCs, stimulating a G-protein coupled phospholipase C (PLC) to produce inositol 1,4,5-trisphosphate (IP_3) and the resultant release of Ca^{2+} from internal stores through inositol 1,4,5-trisphosphate receptors (IP_3R), which is amplified by release of Ca^{2+} through ryanodine receptors (RyRs) (326, 327, 1448, 1574). Subsequent studies of aorta from SMC-specific Ca_V 1.2 knockout mice demonstrated loss of depolarization-induced Ca^{2+} release (419), supporting this hypothesis. In contrast, IP_3R-dependent Ca^{2+} waves in SMCs of rat cerebral arteries appear to be independent of membrane potential (1035). These data suggest that depolarization-induced Ca^{2+} release may not be a general phenomenon.

Vasodilators and L-type VGCCs

Effects of cAMP-PKA signaling on L-type VGCC function—Vasoactive agents such as isoproterenol, adenosine, calcitonin-gene-related peptide (CGRP), and prostacyclin that act through the cAMP-PKA signaling cascade invariably cause relaxation of vascular SMCs and vasodilation. As will be discussed in the sections on K^+ channels, a significant portion

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of their mechanism of action involves the activation of K^+ channels, membrane hyperpolarization and deactivation of VGCCs. In addition, activation of cAMP-PKA signaling pathway in SMCs has been shown to both stimulate and inhibit currents through SMC Ca_V 1.2 channels [see (740) and references therein]. As in cardiac myocytes, the direct effect of cAMP-mediated activation of PKA appears to be stimulatory to SMC Ca_V 1.2 channels (740) (Fig. 3). However, high concentrations of agonists or direct activators of adenylate cyclase, such as forskolin, which result in high levels of cAMP, lead to transactivation of cGMP-activated protein kinase G (PKG) and subsequent inhibition of currents through Ca_V 1.2 channels (740) (Fig. 3). In the heart, Ca_V 1.2 channels are proteolytically processed with cleavage of the distal portion of the C-terminus of the protein, termed the DCT (451). The DCT remains associated with the channel and serves as an autoinhibitor of Ca_V 1.2 (633), requiring association with AKAPs (451). Ca_V 1.2 is similarly processed in cerebrovascular SMCs, and the DCT may play a similar role (89). Phosphorylation of the proximal C-terminal serine 1700 of the DCT relieves this inhibition and results in augmentation of channel activity (444). In neurons and the heart, β-adrenoreceptors, associated trimeric G-proteins, adenyl cyclase, PKA, and protein phosphatases exist in macromolecular complexes with Ca_V 1.2 targeted by AKAPs (302, 312). Studies of SMCs isolated from first-order rat cremaster arterioles and cerebral artery SMCs (1065) also indicate that PKA associates with Ca_V 1.2 (221) suggesting that similar protein complexes are present in the vasculature.

The excitatory action of PKA on L-type VGCCs in vascular SMCs appears counter to the established vasodilator activity of agonists that activate this kinase. However, it is likely that through Ca^{2+}-dependent activation of nearby large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels (514, 891) and/or stimulation of Ca^{2+} sparks (241, 683), PKA-dependent activation of currents through Ca_V 1.2 channels could promote membrane hyperpolarization, be self-limiting and produce vasodilation in arteries and arterioles. In contrast, recent evidence suggests that PKA inhibits currents through Ca_V 3.2 channels in SMCs from rat cerebral arteries (560). The authors suggest that this might reduce intracellular Ca^{2+} and promote vasodilation. However, this same group has shown that Ca^{2+} influx through Ca_V 3.2 channels activates RyRs to produce Ca^{2+} sparks and subsequent activation of nearby BK_{Ca} channels, contributing to the negative feedback regulation of myogenic tone (557) (see BK_{Ca} Channels Section for more on this topic). Inhibition of Ca_V 3.2 activity by PKA would dampen this negative feedback and actually promote vasoconstriction, all other factors constant. Thus, additional research is necessary to clarify the precise mechanism by which PKA modulates the activity of vascular SMC Ca_V 1.2 and Ca_V 3.X VGCCs and how these effects translate into modulation of myogenic tone.

Effects of cGMP-PKG signaling on L-type VGCC function—Activation of PKG inhibits currents through SMC Ca_V 1.2 channels (740) contributing to the vasodilator actions of NO and other cGMP-related vasodilators, although the precise mechanism has not been established (Fig. 3). In cardiac muscle Ca_V 1.2, PKG phosphorylates a number of residues on the α_1 subunit as well as a serine residue on the associated β-subunit (1588). However, site-directed mutagenesis revealed that it is phosphorylation of the channel's β subunit (1588) that mediates inhibition of currents through these VGCCs. It is not known whether

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the inhibitory effects of PKG on SMC Ca_V 1.2 VGCCs are also mediated by phosphorylation of the β subunits found in vascular tissue. Currents through T-type channels also are inhibited by PKG in SMCs from rat cerebral arteries and appear to contribute to the mechanism of dilation of NO and other cGMP-related dilators in this system (558). The molecular mechanism of this inhibition has not been established.

Calcium influx through L-type VGCCs also stimulates Ca^{2+} sparks (241, 389, 678, 683). However, this appears to result from Ca^{2+} loading of the ER rather than from a direct effect of Ca^{2+} entry through L-type channels on underlying RyRs (241, 389).

T-type VGCCs and myogenic tone

The expression and functional role of T-type VGCCs in resistance vessels has been demonstrated in the literature. Whole vessel lysates of first-order Wistar rat cremaster arterioles revealed expression of message for Ca_V 1.2, Ca_V 3.1 and Ca_V 3.2, although the cell type from which the RNA originated was not established (1460). VanBavel et al. (1460) found that myogenic tone in these vessels was potently and efficaciously inhibited by not only the L-type VGCC blocker, verapamil, but also the T-type VGCC blockers Ni^{2+} and mibefradil, supporting a potential role for T-type VGCCs in SMCs from these arterioles. Patch clamp recording of T-type VGCC currents have not been reported in cremaster arteriolar SMCs, only high-voltage-activated currents through VGCCs in SMCs from Sprague-Dawley rats (1552) and golden-Syrian hamsters (266). Furthermore, earlier studies showed that mibefradil dilated cremaster arterioles without reducing intracellular Ca^{2+} suggesting significant off-target effects of this putative T-type VGCC blocker (1171). The effects of Ni^{2+} cannot be so easily dismissed (1460) such that Ca^{2+} entry through T-type VGCCs also may contribute to myogenic tone in rat first-order arterioles. Because verapamil can also block T-type VGCCs, and L-Type VGCCs can be blocked by mibefradil (321), the precise contribution of L- and T-type VGCCs to myogenic tone in these vessels remains to be established. That nifedipine (785, 1171) and diltiazem (185), which are both selective for L-type VGCCs, substantially inhibit myogenic tone in cremaster arterioles, *in vitro*, suggests that L-type channels provide a major contribution (70%–90%) in vessels studied *in vitro*, but the potential for significant regional-, strain-, and species-dependent differences in the contribution of different classes of VGCCs are acknowledged. In mouse cremaster muscle, *in vivo*, in contrast to studies of rat (599) and hamster (670), 60% of resting tone is due to L-type VGCCs, with <20% from T-type VGCCs (628). Inhibition of NO synthesis increased the contribution of T-type VGCCs to ~38% in this model.

In addition to cremaster arterioles (1460), expression and function of T-type VGCCs have also been implicated in mesenteric (173, 521, 692), renal (550) and cerebral (3, 557, 802, 1060) resistance arteries and arterioles. However, many of these studies were based on the use of drugs like mibefradil (1025), which are notoriously non-specific, and patch clamp electrophysiological characterization of the SMCs from the vessels studied is often lacking. In the rat renal afferent arterioles, for example, where expression of Ca_V 3, 1 and 3.2 have been detected in whole vessel lysates (550), and where putative T-type VGCC blockers have been reported to affect myogenic tone and vasoconstrictor reactivity (417, 550), no rapidly inactivating, kurtoxin-sensitive Ca^{2+} or Ba^{2+} current is detected (1312). These data cast

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doubt on a role for T-type channels in rat afferent arterioles. However, alterations in renal function are also observed in Ca_V 3.X-deficient mice supporting a role for T-type VGCCs in renal vascular function in the mouse (1409). It should be noted that Ca_V 3.2 has been detected in endothelial cells in the renal microcirculation (1409) and Ca_V 3.1 in endothelial cells in both mesenteric arterioles (173) and the pulmonary circulation (1646). Thus, indirect effects mediated by changes in endothelial cell function cannot be excluded.

Rapidly-inactivating, nifedipine-insensitive, high voltage-activated Ba^{2+} currents that are inhibited by putative blockers of T-type VGCCs have been demonstrated in SMCs isolated from guinea pig and rat mesenteric arterioles (1032). Similar currents have also been reported in SMCs isolated from branches of rat basilar arteries (802). The molecular identity of these channels has not been established, but it has been speculated that splice variants of Ca_V 3.1 and/or 3.2 may alter the biophysical properties of these VGCCs such that they activate and inactivate at more positive potentials than the full length Ca_V 3.X VGCCs (803). Nifedipine-insensitive currents with the characteristics of T-type VGCCs have also been reported in SMCs isolated from rat middle cerebral arteries (3). Pressure-induced tone of mesenteric arteries from Ca_V 3.1 knock-out mice is inhibited between 40 and 80 mm Hg, supporting a role for T-type VGCCs in myogenic tone at low pressures in these vessels (140). Tone at higher pressures appears dependent on the activity of L-type VGCCs. Studies in rat middle cerebral arteries which express Ca_V 1.2, 3.1, and 3.2 support this hypothesis: at 20 mmHg T-type and L-type VGCCs contribute equally to what little myogenic tone exists at this low pressure, while at 80 mmHg, where there is substantial tone, L-type channels play the dominant role (3). Examination of the pressure-diameter relationship of tibialis anterior feed arteries from mice with SMC-specific knockout of Ca_V 1.2 reveals that pressure-induced tone between 20 and 40 mmHg appears unaffected by the loss of L-type VGCCs (1026). This has been argued as support for a role for T-type channels in myogenic tone at low intravascular pressures (803). Thus, where expressed in combination with L-type VGCCs, T-type VGCCs may contribute to myogenic tone, particularly at low intravascular pressure where SMCs are relatively hyperpolarized.

T-type VGCCs and the negative-feedback regulation of myogenic tone

In rat middle cerebral arteries, Ca_V 3.2 VGCCs participate in the negative feedback regulation of membrane potential and myogenic tone (557, 559). Harraz et al. (557, 559) propose that Ca^{2+} influx through Ca_V 3.2 activates subsarcolemmal RyRs to induce Ca^{2+} sparks, which then activate overlying BK_{Ca} channels to produce membrane hyperpolarization, reducing the activity of Ca_V 1.2 and Ca_V 3.1 VGCCs and limiting myogenic tone (Fig. 4). They also propose that this mechanism may explain the paradoxical loss of vasodilator reactivity that has been observed in vessels isolated from Ca_V 3.2 knockouts (228) or in vessels exposed to low concentrations of Ni^{2+} that selectively block Ca_V 3.2 (1172). However, this mechanism has not been established in other blood vessels.

Other VGCCs in vascular tissue

Rat (549), mouse (552) and human (552) renal afferent arterioles appear to express the α_1 subunits for Ca_V 2.1 P/Q-type VGCCs. Despite expression of Ca_V 2.1 across species, functional differences in channel function are evident: ω-agatoxin dose-dependently inhibits

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K^+-induced constriction in human but not murine intrarenal arteries (552). In cerebral arteries expression and function of R-type VGCCs (Ca_V 2.3) appears after exposure to oxyhemoglobin as occurs during hemorrhagic stroke, contributing to the vasospasm that often occurs after this type of cerebrovascular accident (879).

VGCCs and pathophysiology

Hypertension—There is increased expression and function of Ca_V 1.2 channels in hypertension that contributes to increased myogenic tone and vasoconstrictor reactivity, and decreased vasodilator reactivity, all of which likely contribute to the increase in peripheral vascular resistance that is a hallmark of hypertension (see (716) for numerous references). The mechanisms responsible for the increased number of functional channels expressed in hypertension is not well understood, but may relate to increased trafficking of Ca_V 1.2 α-subunits to the plasma membrane via the increased expression of $\alpha_2\delta_1$ subunits (88) or β_3 subunit (745), and/or altered posttranscriptional processing of the Ca_V 1.2 α_1 subunits by micro-RNAs (miRs) such as miR-328 (518). Altered regulation of Ca_V 1.2 channel function via increased clustering of these channels into macromolecular signaling complexes may also contribute to the channels increased activity in hypertension (1062). In mesenteric artery SMCs from the spontaneously hypertensive rat (SHR), L-type VGCCs display higher current densities, activate at more negative potentials, display a slower inactivation and faster rate of recovery from inactivation than observed in SMCs from Wistar-Kyoto rats (287). Subsequent studies showed that there were significant differences in the expression of $\alpha_2\delta$ and β subunits that likely accounted for the different properties of the VGCC currents recorded in SMCs from the SHR (283). Also, consistent with studies in cerebral arteries (88), the increased L-type current densities recorded in mesenteric SMCs from the SHR were associated with increased expression of the $\alpha_2\delta_1$ subunits (283).

In angiotensin-induced hypertension, there is increased expression of Ca_V 1.2 due to activation of PiP_3K-γ (1470). PiP_3K-γ is activated by the βγ subunits of $G_{12/13}$-protein coupled receptors such as the angiotensin receptor 1 (1335). Activation of PiP_3K-γ promotes trafficking of L-type Ca^{2+} channels to the plasma membrane (1477) that appears to be mediated by PKB/Akt (199, 1470). In addition, phosphorylation of the β subunit of the channel (1477) protects the α_1 subunit from proteolysis, increasing protein stability (1189), which contributes to the increased expression of the channels in the plasma membrane. Inhibitors of PIP_3K-γ blunt angiotensin II-induced hypertension, cause peripheral vasodilation in angiotensin-induced hypertension and reduce the augmentation in Ca^{2+} currents in vascular SMCs from angiotensin-treated animals (199).

Obesity and the metabolic syndrome—Obesity and the metabolic syndrome also appear to cause ion channel remodeling. However, how this impacts VGCC expression and function is not clear. Increased L-type Ca^{2+} channel function was observed in SMCs from obese Zucker rats (1115). Similarly, a high fat diet produced increased Ca^{2+} current densities in cerebral artery SMCs from the Osborne-Mendel rat (1531). Increased resting Ca^{2+} levels and increased constriction to L-type VGCC agonist was observed in coronary vessels from obese swine (157). The expression and activity of L-type VGCCs is upregulated in obese pigs displaying the metabolic syndrome, and blockade of these channels with nifedipine

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increases resting coronary blood flow and exercise-induced increases in flow, whereas this dihydropyridine had no effect on resting flow or functional hyperemia in the hearts of lean pigs (126). In vascular SMCs from diabetic, obese and dyslipidemic *db/db* mice or in cells acutely exposed to elevated glucose, increased Ca_V 1.2-based Ca^{2+} sparklets were observed that resulted from elevated PKA-signaling that required PKA coupling to Ca_V 1.2 via AKAP150 (1065).

In contrast to the studies outlined earlier indicating increased expression and function of VGCCs, it was shown that in miniature pigs fed a high-fat diet to induce obesity and diet-induced hypercholesterolemia, L-type VGCC currents were reduced in SMCs isolated from large coronary arteries, with no effect on currents through these channels in SMCs from coronary arterioles (165). The reasons for these different outcomes is not known, but may be related to regional or species-dependent differences, the time course of the induced metabolic state, and the precise metabolic status of the model that was studied (1348).

Aging—Aging has been shown to impair the development of myogenic tone in murine mesenteric arteries (505). As a test of the hypothesis that a diminished functional expression of L-type Ca^{2+} channels are responsible for this loss of myogenic tone, Ba^{2+} currents through L-type VGCCs were measured (325). Not supporting this hypothesis, aging was found to increase SMC cell size, but did not affect L-type VGCC current density (325).

Diabetes—With the exception of a study of mesenteric artery SMCs from streptozotocin-treated rats that showed no change in L-type VGCC current density (1607), other studies have shown increased expression and function of VGCCs in type 1 diabetes or exposure of vascular SMCs to high glucose levels (421). Increased functional coupling of angiotensin II receptors with L-type Ca^{2+} channels was observed in SMCs from rat thoracic aorta after streptozotocin-induced diabetes (64). Similarly, Ca_V 1.2 function is upregulated by a mechanism involving PiP_3K-δ in streptozotocin-induced diabetes in the mouse and accounts for increased reactivity to phenylephrine that is observed in this model (1160). As noted above, exposure of cerebrovascular SMCs to elevated glucose results in increased L-type VGCC current density, increased clustering of VGCCs and increased Ca^{2+} sparklet activity (1065). Species or regional differences in the adaptation to the diabetic state, time course of development of diabetes and the severity of diabetes may account for the different outcomes that have been observed (1348).

Potassium Channels

Vascular SMCs express a diverse array of K^+ channels that contribute to the regulation and modulation of myogenic tone in resistance arteries and arterioles (40, 270, 332, 403, 520, 630, 665–668, 696, 769, 832, 920, 1000, 1069, 1073, 1074, 1128, 1142, 1187, 1277, 1315, 1397). This includes multiple types of voltage-gated K^+ (K_V) channels, members of the Ca^{2+}-activated K^+ (K_{Ca}) channel family, members of the inward-rectifier K^+ (K_{IR}) channel family, and several types of two-pore K^+ (K_{2P}) channels. The structure, expression and function of K_{2P} channels will not be addressed in the present review (489, 1199, 1283, 1529).

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K_V Channels

Discovery of K_V channels

Currents through K_V channels were first reported by Hodgkin and Huxley in voltage-clamp experiments on the squid giant axon (606, 607). In general, these channels activate in response to membrane depolarization and then inactivate in a voltage-dependent manner with maintained depolarization (489, 688, 1074). There is considerable heterogeneity in the properties of K_V channels found within and among tissues, indicating that there is considerable diversity among the different K_V channels that are expressed (489, 524, 688, 1074). Molecular studies performed over the last 20 years have identified 40 genes encoding mammalian K_V channels representing 12 families (K_V 1–12) that contribute to this heterogeneity (489, 524). Members of the K_V 1–4, 7, and 10–12 form functional channels as homomers, whereas K_V 5, 6, 8, and 9 must coassemble with K_V 2 or 3 subunits to form functional channels (489).

Structure of K_V channels

Each K_V channel is composed of a tetramer of pore forming α subunits (489, 688). Each α subunit has six transmembrane domains, S1–S6. The fourth membrane spanning region, S4, contains the voltage sensor of these channels, and the P-loop between S5 and S6, along with S6 forms the channel pore (82, 489, 687, 797, 1074, 1127) (Fig. 2). The N-terminal portion of the α subunit may be involved in fast (N-type) inactivation that occurs in some forms of these channels (623, 624, 687, 797, 1616). Slow (C-type) inactivation has been linked to the C-terminal domain and resides within or close to the pore of the channel (624, 797). Most K_V channel α subunits are accompanied by modulatory accessory subunits and also interact with numerous proteins in macromolecular signaling complexes [see Gutman et al. (524) for details and references]. Heterogeneity in the function of expressed K_V channels arises not only from the expression of different K_V channel gene products, but also from heteromultimerization of channel subunits, the presence (or absence) of modifier subunits, association of the channels with accessory subunits, alternative splicing, and posttranslational modifications (489, 524).

K_V channels expressed in vascular SMCs

Beech and Bolton (104, 105) and Okabe et al. (1104) were the first to identify currents through K_V channels in vascular SMCs. Subsequent studies have shown their presence in virtually every vascular muscle studied (281, 499, 666, 668, 696, 920, 1074). Like K_V channels expressed in other tissues (688), those in vascular SMCs appear to represent a diverse group of channels with a range of single channel conductances, voltage dependencies, kinetics and pharmacology (1074). Channels in the K_V 1.X family appear to be widely expressed in vascular SMCs. Early studies showed expression of K_V 1.5 in rat vascular SMCs (1120). Subsequent studies by numerous investigators confirmed and extended these findings by showing expression at the mRNA and protein levels of K_V 1.1, 1.2, 1.3, 1.5, and 1.6 in a variety of blood vessels [see Table 5 in Ref. (281) for a summary and original references]. In addition, K_V 2.1 expression has been observed in a number of vessels (281). Expression of members of the K_V 3.X, 4.X, and 9.X also have been reported (281). More recent studies have also demonstrated expression of message (mRNA) and

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protein for members of the K_V 7.X (KCNQ) family of channels (particularly K_V 7.1, 7.4, and 7.5) in SMCs from a number of blood vessels (499, 696, 920).

Pharmacology of vascular SMC K_V channels

As shown in Table 2, K_V channels display a diverse pharmacology, and given the large number of K_V channels expressed in a typical vascular SMC, pharmacological dissection of the function of individual channels, particularly in isolated vessel experiments or *in vivo* is challenging. However, some selectivity exists allowing pharmacological dissection of the function of the complex array of K_V channels that are expressed in vascular SMCs (284, 285). Correolide is selective for K_V 1 family members at micromolar concentrations (414). Derivatives of psoralen (Psora-4 (1472) and PAP-1 (1267), Table 2) are potent, selective inhibitors of members of the K_V 1 family at nanomolar concentrations. However, at micromolar concentrations, these inhibitors also block a number of other K^+ channels (Table 2), such that care must be taken in selection of blocker concentrations. Toxins, such as stromotoxin-1 (K_V 2.1) (387) or phrixotoxins (K_V 4) (335) are particularly useful *in vitro*, but are difficult to implement for *in vivo* experiments due to cost and protein binding issues. Nonetheless, through use of a combination of inhibitors as well as the kinetic analysis of currents in patch clamp experiments, a “fingerprint” can be developed to identify the functional expression of K_V channels that contribute to the regulation of vascular tone in resistance arteries and arterioles (284, 285).

K_V channels and myogenic tone

Early studies demonstrated that K_V channel blockers such as 3,4-diaminopyridine or 4-aminopyridine (4-AP) caused SMCs to contract in a variety of blood vessels (271, 553, 1444), supporting a role for K_V channels in the regulation of vascular tone. It was then shown that millimolar concentrations of 4-AP, a blocker of K_V 1–4 channels (281), inhibited currents around the resting membrane potential of rabbit portal vein myocytes and depolarized SMCs isolated from renal (471) or coronary (830) arteries, indicating that K_V channels contribute to the resting membrane potential of vascular SMCs. Knot and Nelson (763) then showed, in intact, pressurized rabbit cerebral arteries, that 4-AP depolarized SMCs and augmented myogenic tone at intraluminal pressures greater than 40 mmHg, consistent with the hypothesis that 4-AP-sensitive K_V channels contribute to the resting membrane potential and to the negative feedback regulation of myogenic tone. Subsequent studies confirmed these findings in a number of arteries and arterioles (281, 665–668, 1074).

K_V 1 channels in vascular SMCs—The specific K_V channel α-subunits that contribute to the 4-AP-sensitive currents, membrane potential and tone responses have only been examined in a few instances. Cheong et al. (240) found that SMCs in mouse pial arterioles express K_V 1.3, and 1.6, with K_V 1.6 being prominent. Expression of K_V 1.5 was present in perivascular nerves, but not in the SMCs. Consistent with this protein expression pattern they found that agitoxin-2 and margatoxin, peptide blockers of K_V 1.3 and 1.6 channels, constricted arterioles pretreated with endothelin to depolarize the SMCs to about −40 mV. They concluded that K_V 1.3 and 1.6 contribute significantly to 4-AP-sensitive current and regulation of agonist-induced tone. In contrast, in rabbit cerebral arterioles, Cheong et al. (239), found that SMCs express predominantly K_V 1.5 and 1.6. In these cells, currents

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sensitive to the K_V 1 family blocker, correolide, were active at a physiologically relevant membrane potential (−45 mV), and correolide further constricted arterioles preconstricted with endothelin-1. However, agitoxin-2, which blocks channels formed from homomers of K_V 1.6, had no effect on currents or vascular tone. These data led the authors to suggest that channels formed from heteromers of K_V 1.5 and 1.6 composed the 4-AP and correolide-sensitive currents in these vessels. In rabbit portal vein myocytes, based on the biophysical properties and pharmacology of native current compared with heterologously expressed K_V 1.2 and 1.5, Kerr et al. (741) suggested that the 4-AP-sensitive currents in these vascular myocytes arose from heteromers of K_V 1.2 and 1.5. Subsequent expression and immunoprecipitation studies supported this hypothesis (1406). Alberwani et al. (28) came to a similar conclusion and reported expression of message and protein for K_V 1.2 and 1.5 in rat cerebral arteries. Correolide inhibited currents at physiological membrane potentials, depolarized SMCs in pressurized arteries and constricted these vessels consistent with a major role for K_V 1 channels in the negative feedback regulation of myogenic tone. Based on the biophysical and pharmacological properties of the native channels and their finding that K_V 1.2 and K_V 1.5 coimmunoprecipitated, they concluded that the correolide-sensitive currents originated from heteromers of K_V 1.2 and 1.5. Using dialysis of cells with anti-K_V channel subunit antibodies, it was proposed that K_V currents in rat mesenteric arteries were composed of currents through K_V 1.2, K_V 1.5, and K_V 2.1 (909). Dialysis with an anti-K_V 1.3 antibody was without effect despite a prior report of expression of these channels in rat mesenteric artery SMCs (1564). In another study of rat mesenteric resistance arteries, based on the channel expression profile, the biophysical properties and the pharmacology, it was proposed that heteromers of K_V 1.2, K_V 1.6, and K_V 1.5 composed the 4-AP and correolide-sensitive currents that were responsible for negative feedback regulation of myogenic tone (1163). Chen et al. (231) then showed that in rat middle cerebral arteries, overexpression of K_V 1.5 dampened myogenic tone, whereas expression of loss-of-function mutants of this channel enhanced myogenic tone consistent with a major role for K_V 1.5 in whatever native channels are expressed in these cells. Rat retinal arterioles display rapidly inactivating (A-type) K_V currents (976, 977), in contrast to the slowly inactivating delayed rectifier-type currents observed in most vascular SMCs (281, 665–668, 1074). However, as with the other vessels types presented thus far, K_V 1.5-based channels appear to play a major role, because the currents were inhibited by correolide or intracellular application of an anti-K_V 1.5 antibody (976). McGahon et al. found coexpression of $K_V\beta1$ accessory subunits in these vessels, which may account for the kinetics of the currents observed in SMCs from retinal arterioles (976). Rapidly inactivating A-type currents also have been observed in SMCs from rabbit portal veins (106), human mesenteric arteries (1311), rat renal microvessels (494), and rabbit aorta (541). However, the molecular constituents of these channels have not been ascertained. In mouse mesenteric arteries, mRNAs for K_V 1.1, 1.2, 1.3, 1.5, 1.6, 2.1, 3.3, 3.4, 4.1–4.3, and K_V 9.3 along with a number of accessory subunits were detected by PCR using TaqMan low density arrays, with message for K_V 1.2, 1.5, 1.6, and 2.1 being most prominent (1028). Pharmacological dissection of K_V channel currents in patch clamp studies demonstrated major contributions from K_V 1 (56% at +80 mV) and K_V 2 (27% at +80 mV) channels similar to what has been reported in mesenteric arteries from other species (see earlier).

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K_V 2 channels in vascular SMCs—As noted earlier, currents through K_V 2.1 channels also appear to be functional in resistance arteries and arterioles. Rat cerebral artery SMCs express K_V 2.1, and stromatoxin, which blocks this class of K_V channels, inhibits whole-cell currents and enhances myogenic tone suggesting that these channels contribute to the regulation of membrane potential and the negative feedback of myogenic tone in these vessels (44). In rat middle cerebral artery, K_V 2.1 may form heteromeric channels with K_V 9.3 and be particularly important in regulation of resting membrane potential at negative membrane potentials associated with low intravascular pressure (1642). Rat and mouse mesenteric arteries also express K_V 2.1 that contributes to whole-cell K_V currents in these vessels (909, 1028).

K_V 7 channels in vascular SMCs—Members of the K_V 7 family also appear to contribute to resting membrane potential and the negative feedback regulation of myogenic and vasoconstrictor-induced tone in several vessels (499, 696, 920). Ohya et al. (1102) reported that only K_V 7.1 was expressed in SMCs from portal vein and showed that the K_V 7 channel blocker, linopirdine (23), significantly inhibited whole-cell currents in these cells and increased the duration of evoked action potentials. Subsequent studies utilizing additional K_V 7 antagonists confirmed and extended these studies to show that K_V 7 channels control electrical excitability of murine portal vein myocytes (1598) and that K_V 7.4 and 7.5 are also expressed in SMCs of this vessel (1600). In SMCs from murine aorta, carotid artery, femoral artery and mesenteric arteries, K_V 7.1, 7.4, and 7.5 mRNA was detected, and expression of protein for these isoforms was confirmed in SMCs from aorta (1599). Yeung et al. (1599) also found that K_V 7 channel blockers constricted the vessels, whereas retigabine, which activates K_V 7 channels, relaxed preconstricted vessels. These data support a significant role for K_V 7 channels in the regulation of membrane potential in vascular SMCs. In cerebral arteries, K_V 7 channels appear to contribute to the negative feedback control of myogenic tone, because inhibitors of these channels enhance myogenic tone at pressures greater than 20 mmHg (1643). These SMCs also were shown to express K_V 7.1, 7.4, and 7.5 (1643). SMCs in rat coronary arteries also express K_V 7.1, 7.4, and 7.5 (744). Blockade of K_V 7.1 with HMR 1556 had no effect on resting tone of these vessels, whereas application of pan-K_V 7 blockers contracted the vessels supporting a role for K_V 7.4 and 7.5 in the regulation of resting membrane potential. Consistent with this hypothesis, selective activators of K_V 7.2–7.5 relaxed preconstricted vessels, whereas an activator of K_V 7.1 was without effect. Supporting the findings from isolated coronary arteries, application of K_V 7 blockers to Langendorff-perfused hearts increased vascular resistance indicating a significant role for K_V 7 channels in the regulation of coronary vascular tone. In coronary arteries K_V 7.1 does not appear to play a significant functional role (744). A selective activator of K_V 7.1, R-L3 (1236), relaxes preconstricted rat mesenteric arteries, although blockade of these channels has no effect on resting or agonist induced tone (215). As pan-K_V 7 channel blockers contract rat mesenteric arteries (215, 695), these data suggest that there may be distinct roles for K_V 7 channel isoforms in different regions of the vasculature. In rat cerebral arteries, both K_V 7.4 and 7.5 appear to contribute to the negative feedback regulation of myogenic tone particularly at low intravascular pressures (214). Expression and function of K_V 7.4 SMCs in rat mesenteric arteries require expression of and colocalization with the auxiliary subunit KNCE4 (694). These channels also interact with G-

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protein βγ subunits, that appear to be required for channel activity and participate the in the regulation of myogenic tone in rat renal arteries (1342).

Vasoconstrictors and K_V channels

Vasoconstrictors modulate the activity of K_V channels. Given the voltage dependence of these channels, one would expect that vasoconstrictors that depolarize vascular SMCs should activate K_V channels (Fig. 5). Thus, depolarization-induced activation of K_V channels should limit the degree of SMC depolarization, and hence vasoconstriction, in a negative feedback manner. Consistent with this hypothesis it has been shown that block of K_V channels potentiates constriction induced by $G_{q/11}$-coupled receptor agonists (214, 239, 240, 271, 540, 949, 1124, 1300).

Kinase-mediated inhibition of K_V channels—However, evidence also suggests that K_V channel closure may contribute to the mechanism of action of vasoconstrictors. Agents such as phenylephrine (1012), 5-HT (78, 770, 1360), and angiotensin II (263) inhibit vascular SMC K_V channels (Fig. 5). This closure may involve protein kinase-mediated or Ca^{2+}-dependent inhibition of K_V channels (Fig. 5). Activation of PKC, either by phorbol esters (18) or by $G_{q/11}$-coupled receptor agonists (263, 571, 770) inhibits currents through 4-AP-sensitive K_V channels, which should contribute to vasoconstrictor-induced SMC depolarization (Fig. 5). In pulmonary vascular SMCs, 5-HT inhibits 4-AP-sensitive K_V currents through a mechanism involving PKC and a tyrosine kinase via a mechanism that involves channel internalization (265). A similar mechanism may be involved in peripheral arteries, because 5-HT inhibits 4-AP-sensitive currents to mediate contraction of mesenteric arteries through a mechanism involving the tyrosine kinase, c-SRC (1360) in addition to PKC (770) (Fig. 5). Active PKC also inhibits currents through K_V 7 channels, and this PKC-dependent inhibition of current has been shown to depolarize SMCs and lead to contraction of rat mesenteric arteries to low concentrations of arginine vasopressin (919). In rat cerebral arteries, uridine triphosphate (UTP), and U46619 inhibit 4-AP-sensitive K_V currents through a mechanism involving Rho-kinase and modulation of the actin cytoskeleton that is independent from PKC (912, 913) (Fig. 5). Vasodilators that act through the cAMP and cGMP signaling cascades may act, in part, by antagonizing this Rho-kinase-mediated K_V channel downregulation (914).

Calcium-mediated inhibition of K_V channels—In addition to kinase-mediated inhibition of currents through K_V channels, agonist-induced increases in intracellular Ca^{2+} concentration also have been shown to inhibit 4-AP-sensitive K_V channel activity (289, 471, 657) (Fig. 5). Both the kinase-dependent and Ca^{2+}-dependent processes would provide a positive feedback signal and could support depolarization and constriction for vasoconstrictors that activate PKC or Rho-kinase and/or raise intracellular Ca^{2+}.

Vasodilators and K_V channels

cAMP-PKA-mediated activation of K_V 1 channels—A number of vasodilators have been proposed to act, in part, by activation of K_V channels in the membrane of vascular SMCs. Dilators that act through the cAMP-PKA pathway were shown to activate 4-AP-sensitive K_V channels in rabbit vascular SMCs (19–21) (Fig. 5). Subsequent studies by other

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investigators indicated a significant role for 4-AP-sensitive K_V channels in the mechanism of action of vasodilators that act on G_s-coupled receptors to activate adenylate cyclase, increase the production of cAMP, and activate PKA (128, 331, 336, 577, 578, 849, 1254). Phosphorylation of K_V 1.2 by PKA at serine 449 in the C-terminus of this channel mediates the increase in whole-cell currents (710), which may underlie the 4-AP-sensitive effects of cAMP-PKA-related vasodilators in vessels where heteromers of K_V 1.2 and 1.5 or 1.6 predominate (28, 231, 741, 1163, 1406). In rat cerebral artery SMCs, PKA-dependent phosphorylation of K_V 1.2 depends on interaction of the channels with the scaffolding protein PSD95, which may be involved in targeting PKA to K_V 1.2 (1024).

cAMP-PKA-mediated activation of K_V 7 channels—The cAMP-PKA signaling pathway also modulates the activity of K_V 7 channels. In rat renal arteries the β-adrenoreceptor agonist, isoproterenol, or the adenylate cyclase activator, forskolin, activate currents through K_V 7 channels to dilate these vessels, and siRNA knockdown of K_V 7.4 attenuated these responses (216). The C-terminus of K_V 7 channels has binding domains for AKAPs (536), consistent with the idea that vascular K_V 7 channels may exist in signaling domains with PKA (216). Activation of K_V 7.4 channels by isoproterenol involves G-protein βγ subunits in rat renal arteries (1342).

Adenosine-induced dilation of coronary arteries also appears to be mediated in part by K_V 7.4 (744). Vasodilation of rat cerebral arteries induced by CGRP is inhibited by the pan-K_V 7 blocker linopirdine, but not 4-AP (214). Furthermore, siRNA knockdown of K_V 7.4, but not K_V 7.5 also inhibited CGRP-induced vasodilation indicating a major role for K_V 7.4 in the mechanism of action of CGRP in rat cerebral arteries. Thus, agonists that act at G_s-coupled receptors also modulate the activity of K_V 7 channels in the vasculature.

NO-cGMP-PKG-mediated activation of K_V channels—Early studies suggested roles for 4-AP-sensitive K_V channels in various aspects of endothelium-dependent vasodilation in several vascular beds (370, 589, 1299, 1612). However, subsequent studies showed that inhibitory effects of 4-AP likely resulted from depolarization-induced effects on myoendothelial electrical coupling, rather than blockade of effects of endothelium-derived autacoids on 4-AP-sensitive K_V channels in SMCs (36, 519, 588, 1299). Nonetheless, endothelium-dependent dilation or dilation induced by NO or cGMP analogs are inhibited by K_V channel blockers in rat basilar arteries (1317) (Fig. 5). Studies in rat aortic SMCs indicated that NO and atrial natriuretic peptide-induced relaxation can be inhibited by high concentrations of 4-AP and tetraethylammonium (TEA), and that these dilators activate K_V channel currents in aortic A7R5 cells that appear to be carried by K_V 2.1 containing channels (1384). Sodium nitroprusside (SNP)-induced dilation of canine coronary circulation is inhibited by 4-AP or correolide suggesting a role for K_V 1 channels in NO-mediated vasodilation (331). More recently, cGMP has been shown to increase currents through K_V 7 channels. Blockade of these channels inhibits relaxation of rat renal arteries induced by atrial natriuretic peptide, and of rat aorta induced by atrial natriuretic peptide or SNP, both of which act through the cGMP-signaling cascade (1341). In contrast, SNP-induced relaxation of porcine coronary arteries is unaffected by K_V 7 channel blockade (579). Thus, there may be species and regional differences.

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Other dilators that activate K_V channels—In addition to NO, endothelium-derived hydrogen sulfide (H_2S) (223, 946, 1262) and hydrogen peroxide (H_2O_2) (1210) also have been proposed to act, in part, via activation of SMC K_V channels (Fig. 5). Hydrogen sulfide-induced relaxation and SMC hyperpolarization of rat aorta are blunted by 4-AP suggesting a role for K_V channels in the mechanism of action of this dilator (223). Other studies suggest that H_2S activates vascular SMC K_V 7 channels to hyperpolarize and relax the SMCs (946, 1262). Hydrogen peroxide activates 4-AP-sensitive K_V channels in SMCs from canine coronary (1210) and rat mesenteric (1135) arteries. Importantly, 4-AP also inhibits H_2O_2-induced relaxation of canine coronary (1210, 1211) and rat mesenteric (1135) arteries, dilation of isolated canine coronary arterioles, and the H_2O_2-induced increase in coronary blood flow, *in vivo* (1211). The effects of H_2O_2 on K^+ currents and SMC tone can be inhibited by dithiothreitol (DTT), suggesting that the effects of H_2O_2 on K_V channels involve thiol oxidation (1135, 1210, 1211). In mesenteric arteries, the effects of H_2O_2 may involve S-glutathionylation of K_V channels, with K_V 2.1 being a likely target (1135).

Voltage-gated K^+ channels also may serve as sensors mediating hypoxia- and acidosis-induced dilation in coronary arteries. Hypoxia-induced relaxation of porcine coronary arteries is inhibited by K_V 7 channel blockers, and hypoxia activates currents through K_V 7 channels in SMCs from these vessels (579). It has also been shown that acidosis activates 4-AP-sensitive K_V channels in coronary vascular muscle cells (119), although the functional significance of this effect was not studied.

Perivascular adipose tissue release one or more anticontractile substances, often referred to as adipocyte-derived relaxing factors that appear to activate K_V 7 channels (1389). In resistance arteries upstream from the microcirculation of the gracilis muscle in the rat, this seems to involve K_V 7.4 (1624).

Functional vasodilation and K_V channels

The role played by vascular K_V channels in the local regulation of blood flow is not clear. Functional hyperemia is impaired and resting blood flow reduced by 4-AP in canine hearts, *in vivo*, supporting a role for 4-AP-sensitive K_V channels in coupling metabolism to blood flow (125, 1233). Also, the duration of reactive hyperemia is impaired by 4-AP in this model (331). Similarly, the K_V 1 channel blocker correolide inhibited dobutamine-induced hyperemia at every level of myocardial oxygen consumption and also impaired reactive hyperemia in anesthetized pigs (492). In pigs, 4-AP also impairs reactive hyperemia (126), but does not affect blood flow autoregulation (127). Also, in contrast to the findings in dogs (1233) and the correolide studies in pigs (492), 4-AP had no effect on the relationship between myocardial oxygen consumption and coronary blood flow suggesting that there may be model-dependent differences in the role played by K_V channels (127). In Langendorff-perfused rat hearts, K_V 7 channel blockers increase resting vascular resistance and inhibit reactive hyperemia (744). However, pacing-induced functional hyperemia and blood flow autoregulation are unaffected (744). In the coronary circulation of pigs, block of K_V 7 channels with linopirdine had no effect on resting blood flow, or the increase in blood flow after ischemia, H_2O_2 or exercise despite evidence for expression and function of these channels in coronary SMCs from this model (491). Thus, there appears to be species or

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model-dependent differences in the participation of K_V channels in the local regulation of blood flow in the heart. In skeletal muscle, exercise training is accompanied by an increase in the functional expression of K_V channels in resistance arteries (709), but their function in the local regulation of blood flow was not studied.

K_V channels and pathophysiology

Hypertension—The effects of hypertension on K_V channel expression and function are not clear (280, 290, 716, 771). Electrophysiological studies have reported increased (282, 286), decreased (170, 171, 279, 288, 886, 947, 1414), or no change (887, 890) in K_V current density. One possible explanation for these differences relates to the experimental conditions used to study K_V currents; examination of studies on SMCs from the same vessel, recorded in the same lab are particularly illuminating (282, 288). In SMCs from mesenteric arteries, K_V channel currents recorded using conventional whole-cell methods with intracellular Ca^{2+} buffered to low levels with 10 mmol/L 1,2-Bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid tetrakis (BAPTA), 4-AP-sensitive K_V currents were observed to be higher in cells from SHR than from Wistar-Kyoto (WKY) rats (282). In contrast, in the same cells studied using the perforated-patch method in which intracellular Ca^{2+} is not buffered, K_V channel current density was reported to be lower in cells from SHR versus WKY (288). As increased intracellular Ca^{2+} inhibits K_V channels (289, 471, 657), this could explain why opposing results were obtained in the same SMCs and rat model of hypertension. Regional differences in the impact of hypertension on K_V channel expression and function as well and differences in the model of hypertension used, also may contribute to the varied reports in the literature.

As with electrophysiological studies, examination of mRNA and protein expression of K_V channels in models of hypertension also has led to conflicting results. Cox (282, 286) has reported an increase in mRNA for K_V 1.2, K_V 1.5, and K_V 2.1 that is supported by increased protein expression for these K_V channel subunits by Western blot and increased K_V channel current densities in patch clamp experiments of mesenteric artery from SHR versus WKY (282, 286). It is worthy to note that examination of mRNA and protein for K_V channel subunits in aortic SMCs revealed no difference in expression between SHR and WKY (286). These data support the idea that there are regional differences in the effects of hypertension on ion channel expression.

In support of the hypothesis that K_V channel function is upregulated in hypertension, it has been reported that 4-AP or 3,4 diaminopyridine causes an immediate increase in peripheral vascular resistance that is greater in SHR than in WKY, and was attributed to closure of K_V channels on vascular SMCs (117). However, these data are difficult to interpret, because of the concomitant upregulation of VGCC expression and function, as outlined in the section on VGCCs in hypertension.

In contrast to the studies reporting upregulation of K_V channel expression and function in hypertension, several investigators have found decreased expression and function of K_V channels in vessels from hypertensive animals. Both whole-cell K_V currents measured using the perforated patch technique, and K_V 1.2 and K_V 1.5 protein expression were lower in mesenteric arteries from 6 to 8 month old SHR versus WKY (1628). In superior mesenteric

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arteries, membrane potential was more depolarized in vessels from rats with L-NAME-induced hypertension (170). This was accompanied by decreased protein expression for K_V 1.5 (170), and decreased K_V channel current densities (171). In two forms of hypertension, there was a reduced protein expression of K_V 1.2 and 1.5, decreased whole-cell K_V currents in SMCs and reduced functional role of K_V 1.X channels in the regulation of myogenic tone in rat cerebral arteries (1414). The protein expression for K_V 1.2 and 1.5 were reduced in aortas of SHR versus WKY (860). These changes were correlated with reduced contraction induced by 4-AP, maurotoxin, and mephetyl tetrazole, inhibitors of K_V 1.2 and 1.5 channels, respectively. In a mouse model of hypertension, decreased K_V channel current densities were observed in patch clamp studies of SMCs isolated from mesenteric arteries from BPH (Blood Pressure–hypertensive) versus BPN (Blood Pressure–normotensive) mice (1028). Currents in cells from BPN were predominantly due to K_V 1, K_V 2, K_V 4, and K_V 3 channels in order of decreasing importance. In cells from BPH, the proportional contribution from K_V 1 channels was similar to those in cells from BPN, whereas there was a reduced contribution of currents through K_V 2 channels. K_V 2 currents were also slower to activate and deactivate. Intracellular application of an anti-K_V 6.3 antibody, which is expressed only in cells from BPH, decreased K_V 2 currents that could be reproduced by expression of both K_V 2.1 and 6.3 in HEK293 cells suggesting heteromerization of these channels. BPH cells were more depolarized and guangxitoxin (selective K_V 2 blocker) produced less depolarization in BPH cells consistent with the expression of K_V channel heteromers in the cells from BPH. The decreased expression of K_V 1 channels that was observed could be due to decreased expression of the K^+ channel-associated protein (KChAP), a chaperone for these channels.

K_V 7.4 protein expression and function are reduced in thoracic aorta and mesenteric arteries from SHR and angiotensin-induced hypertensive mice compared with vessels from normotensive counterparts (695). Decreased protein expression and function of K_V 7.4 in mesenteric arteries from SHR was also observed by Zavaritskaya et al. (1624). Loss of K_V 7.4 also accounts for reduced β-adrenoreceptor-mediated dilation of renal arteries in SHR (216). However, in the gracilis artery, K_V 7.4 expression and function does not seem to be altered in the SHR (1624).

In cerebral arteries of rats, angiotensin II-induced hypertension, independent from the increase in blood pressure, resulted in decreased expression of K_V 2.1 protein and a reduction in whole-cell K_V channel currents (42). The reduced expression was mediated by activation of the transcription factor, Nuclear Factor of Activated T-cells C3 (NFATC3) through a pathway that involves Ca^{2+} influx through L-type VGCCs and activation of calcineurin (42). It was also shown that K_V 2.1 function is reduced, with no change in K_V 1 function in angiotensin II-induced hypertension (44). Thus, the bulk of the literature seems to support the hypothesis that there is reduced K_V channel expression and function in hypertension. However, the specifics may depend on the vascular bed examined, the model of hypertension studied and the duration and extent of hypertension.

Obesity and the metabolic syndrome—As in models of hypertension, there is evidence for both increased and decreased expression and function of K_V channels in models of obesity and the metabolic syndrome. Hypercholesterolemia also impairs K_V

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channel function in coronary SMCs (332, 1581). In pigs with diet-induced metabolic syndrome, coronary artery K_V channel expression and function are impaired and correlate with the impairment in metabolic vasodilation in this model (125). There is selective downregulation of K_V 2.1 expression and function in both cerebral and mesenteric arteries that contributes to enhanced arterial tone in mice fed a high fat diet (1083). The decreased expression and function of K_V 2.1 is mediated by calcineurin-dependent activation of the transcription factor NFATC3 that is associated with AKAP150 (1083).

In contrast, in Otsuka Long-Evans Tokushima fatty (OLETF) rats, the reactivity of mesenteric arteries to 5-HT is enhanced compared the reactivity of vessels from Long-Evans Tokushima Otsuka (LETO) rats (770). It was found that 4-AP-sensitive K_V currents were higher in SMCs isolated from OLETF rats compared to SMCs from LETO rats, and importantly, that 5-HT inhibited K_V channel currents in SMCs from OLETF rats to a greater extent via a mechanism involving PKC (770). There is increased reactivity to 4-AP in aortas from atherosclerosis-prone mice suggesting K_V channel function is augmented in aortic SMCs (704). Thus, as with hypertension there appears to be heterogeneity in the effects of obesity and the metabolic syndrome on K_V channel expression and function.

Aging—In Fisher 344 rats K_V 1.5 protein expression is unchanged with advanced age, but in soleus muscle feed arteries 4-AP induced constriction is increased in vessels from aged rats suggesting increased function of K_V channels (730). In soleus muscle feed arteries, the K_V 1 selective inhibitor, correolide had similar effects (475). These data suggest that there may be regional differences in the impact of aging on expression and function of K_V channels. Subsequent studies showed that exercise training could reverse the effects of aging on K_V 1 channel function in soleus feed arteries (475).

Diabetes—In experimental models of type 1 diabetes, there appears to be a decreased expression and function of K_V channels that may contribute to the increased vascular reactivity observed in this disease (771). High glucose impairs K_V channel function in coronary arteries (852, 892) by nitration of K_V channels (852). Exposure of coronary arteries to high glucose impairs cAMP-mediated vasodilation by impairing the function of K_V channels (849). Similarly, dilation induced by cAMP-related vasodilators is impaired in coronary arteries isolated from streptozotocin-treated rats due to reactive oxygen species (ROS)-related impairment of K_V channel function (181). Exposure of SMCs isolated from mesenteric arteries from Wistar rats to elevated glucose reduces K_V channel currents, depolarizes the SMCs and inhibits endothelin-induced inhibition of the K_V current that remains through a mechanism that involves PKC (1192). Streptozotocin-induced diabetes is associated with decreased K_V channel current densities and impaired cAMP-mediated dilation in rat coronary arteries (217). Protein expression of K_V 1.2 but not K_V 1.5 is reduced in coronary arteries from these streptozotocin-treated rats (218).

Other disease states—Vasospasm associated with subarachnoid hemorrhage results, in part, from oxyhemoglobin-induced activation of tyrosine kinases that stimulate endocytosis of K_V 1.5 channels, a reduction in K_V currents, the resultant depolarization of cerebrovascular SMCs and activation of VGCCs in the rabbit (655). Reduced K_V channel

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function is also observed in dog models of subarachnoid hemorrhage (685) that may be related to decreased expression of K_V 2 channel subunits (22, 685).

Ca^{2+}-activated K^+ Channels

Discovery of Ca^{2+}-activated K^+ channels

Calcium-activated K^+ (K_{Ca}) channels are a group of ubiquitous, abundant K^+ channels that are activated by increases in intracellular Ca^{2+} concentration (602, 822). They are the most abundant K^+ channels found in the membrane of most cells, including vascular SMCs (1074). The first evidence for K_{Ca} channels came from the observation that chelation of Ca^{2+} in red blood cells inhibited the release of K^+ ions during metabolic inhibition (464). This was followed by microelectrode studies in which the K^+ conductance of molluscan neurons was shown to increase after they were injected with solutions containing Ca^{2+} (986, 987). Subsequent patch clamp studies in the early 1980s by numerous investigators showed that K_{Ca} channels were found in essentially all cells (602, 822). Two general classes of K_{Ca} channels were originally identified and named based on their single channel conductances, voltage sensitivities and pharmacology: large conductance Ca^{2+}- and voltage-activated BK_{Ca} channels and small conductance Ca^{2+}-activated K_{Ca} (SK_{Ca}) channels (602, 822). Subsequent molecular studies identified the KCNMA1 gene that encodes the α-pore-forming subunit of BK_{Ca} channels (K_{Ca} 1.1) (187, 1126), and KCNN1–3 (774) and KCNN4 (656, 713) genes that encode the α-subunits for K_{Ca} 2.1–2.3, small conductance, apamin-sensitive SK_{Ca} channels and K_{Ca} 3.1, the intermediate conductance, IK_{Ca} channel, respectively (1509). The focus in this section will be on BK_{Ca} channels as only two studies have identified SK_{Ca} channels in vascular SMCs from systemic blood vessels (468, 646), and IK_{Ca} channels appear only to be expressed in proliferating SMCs (135, 1077, 1402, 1421).

BK_{Ca} Channels

Structure of BK_{Ca} channels

The pore-forming, α subunit of BK_{Ca} channels has seven transmembrane spanning domains (S0–S6), with the pore formed by the P-loop between S5 and S6, and the S6 domains (989). What differentiates BK_{Ca} channels from other members of the K_V family is the presence of an additional transmembrane spanning region (S0) at the NH_2-terminus of the molecule and a long C-terminus cytoplasmic tail region (989). Positively charged residues in S2, S3 and S4 serve as the voltage sensors in BK_{Ca} channels (916), less centralized than in the S4-segment of K_V channels. Residues in two, tandem regulator of conductance of K^+ (RCK) domains (RCK1 and RCK2) in the large cytosolic C-terminus of the α subunit serve as the Ca^{2+} sensors of the channel (see (621) for refs). The α subunit of BK_{Ca} channels is subject to considerable alternative splicing, with greater than 20 spliced variants identified (13, 810, 1431, 1561, 1578). This allows considerable functional diversity among BK_{Ca} channels expressed in different tissues and also allows for dynamic regulation of BK_{Ca} channel function (1561, 1578).

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Association with β_1 subunits

The α subunit of BK_{Ca} channels often associates with modulatory β subunits; of the four genes (KCNMB1–4, encoding K_{Ca}β1–4 subunits), K_{Ca}β1 appears to be the main isoform expressed in vascular SMCs, altering channel gating kinetics and increasing the Ca^{2+} sensitivity of the α-subunit (974, 982, 988, 1432). Association of the α subunit with β1 is required for activation of BK_{Ca} channels by agonists such as dehydrosoyasaponin I (982) and 17β-estradiol (1454). Variation in the degree of coupling of α and β subunits may explain, in part, the heterogeneity of Ca^{2+} sensitivity of BK_{Ca} channels between and within vascular SMCs from various sources (1382) (see later for more on this topic). Studies in rat cerebral artery SMCs show that while most of the α subunits of BK_{Ca} channels reside in the plasma membrane, the β1 subunits are located in Rab11A-positive recycling endosomes and can rapidly traffic to the plasma membrane to associate with the α subunits, providing a dynamic means to regulate the function of BK_{Ca} channels (842).

LRRCs as BK_{Ca} channel subunits

In addition to β subunits, the α subunit of BK_{Ca} channels also associates with leucine-rich-repeat-containing proteins (LRRCs) that have been suggested to be γ subunits of BK_{Ca} channels (37, 391, 490, 1576). These LRRCs increase the voltage sensitivity of the channels allowing activation of BK_{Ca} channels at negative membrane potentials in the absence of Ca^{2+} (490, 1576). The presence of LRRCs also increases the sensitivity of the channels to activators such as docosahexaenoic acid (622). In vascular SMCs from rat cerebral arteries, LRRC26 appears to be the isoform expressed (391). Small interfering RNA knock down of LRRC26 increased myogenic tone, reduced constriction induced by the BK_{Ca} channel blocker, iberiotoxin, and reduced dilation induced by the BK_{Ca} channel activator, NS-1619 (391) supporting a functional role for this auxiliary subunit. The expression and function of LRRCs in other vascular SMCs has not been established.

K_{Ca} channels expressed in vascular SMCs

Benham et al. (1514) were among the first to identify BK_{Ca} channels in patch clamp studies of vascular SMCs isolated from guinea pig mesenteric arteries. They found a high density of Ca^{2+}- and voltage-sensitive K^+ channels in inside-out patches of membrane with a single channel conductance of ~200 pS in symmetrical 126:126 mmol/L K^+ solution. Subsequently, numerous investigators have reported similar findings (1074). These studies indicate that vascular muscle cells from a variety of large systemic blood vessels express BK_{Ca} channels with single channel conductances of ~250 pS in inside-out patches of membrane exposed to symmetrical 140 to 150 mmol/LK^+ solutions (198, 981, 1074). Similar findings were reported for arteriolar SMCs from rat and hamster cremaster muscle (672) and rat kidneys (468). Thus, BK_{Ca} channels appear to be ubiquitously expressed in systemic vascular SMCs.

Calcium-activated K^+ channels of smaller conductance (SK_{Ca}) have also been reported (468, 646). In cells from rabbit portal vein, a K_{Ca} channel with a single channel conductance of 92 pS in symmetrical 142 mmol/L K^+ that is insensitive to extracellular TEA has been reported (646). The sensitivity of these channels to other pharmacological agents was not evaluated. Gebremedhin et al. (468) reported an apamin-sensitive K_{Ca} channel present in the

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membranes of rat renal arteriolar muscle cells with a unitary conductance of 68 pS in symmetrical 145 mmol/L K^+. In both of these instances, BK_{Ca} channels were also identified. These data suggest that SK_{Ca} channels may be present in the membrane of some vascular SMCs.

Pharmacology of BK_{Ca} channels

As shown in Table 2, BK_{Ca} channels display a distinct pharmacological profile that has allowed pharmacological dissection of their function, even in *in vivo* experiments. Both iberiotoxin and paxilline, for example are very selective for BK_{Ca} channels (1509). However, caution must be used with charybdotoxin and TEA, because these blockers affect several other channels that may be expressed in vascular smooth muscle (Table 2). Charybdotoxin blocks IK_{Ca} channels, K_V 1.2 and K_V 1.6 in addition to BK_{Ca} channels (Table 2). In some systems, TEA, at concentrations of 1 mmol/L or less, is quite selective for BK_{Ca} channels. However, TEA also potently blocks K_V 1.1, K_V 1.2, and K_V 3.1, channels also expressed in some vascular SMCs (Table 2).

BK_{Ca} channels and myogenic tone

Evidence for BK_{Ca} channels in the negative-feedback regulation of myogenic tone—Early studies showed that inhibitors of BK_{Ca} channels (charybdotoxin, iberiotoxin, or millimolar concentrations of TEA) depolarized vascular SMCs and constricted small, myogenically active rabbit cerebral arteries when they were pressurized, *in vitro* (175, 1071). Similar results have been reported in a large number of different preparations studied by pressure myography including rat tail arteries (1270), rat saphenous arteries (116), rabbit renal arcuate arteries (1176), canine subepicardial arteries (191), canine coronary arterioles (1210), first-order hamster (1596) or rat cremaster arterioles (629, 785), rat small mesenteric arteries (677, 911), hamster (1528), or murine (1527) cremaster muscle feed arteries and second-order arterioles, and murine superior epigastric arteries (573). Charybdotoxin contracts rings of porcine coronary arteries (467) and strips of rat femoral and mesenteric arteries (65) and enhances stretch-induced myogenic tone of dog basilar (66), middle cerebral (65), posterior cerebral (65), and coronary (65) artery strips. However, strips of canine mesenteric artery (65) and rat carotid artery (65) did not respond to this BK_{Ca} channel blocker, likely because they did not display stretch-induced myogenic tone. Resting membrane potential of porcine coronary arteriolar SMCs is not affected by iberiotoxin, but stretch-induced depolarization of these cells is potentiated in the presence of this BK_{Ca} channel blocker supporting their role in the negative feedback regulation of myogenic tone (1549). Both TEA (5 mmol/L) and charybdotoxin depolarize SMCs in rat superior mesenteric arteries (225).

The *in vitro* data cited earlier suggest that BK_{Ca} channels are active under resting conditions, contribute to resting membrane potential and participate in the negative feedback regulation of myogenic tone. *In vivo* studies of canine diaphragm have demonstrated that the BK_{Ca} blocker, iberiotoxin, decreases resting blood flow when infused into the blood perfusing this muscle (1462, 1463). These data suggest that BK_{Ca} channels may play a role in the regulation of resting blood flow in the canine diaphragm. However, these and all *in vivo* data must be interpreted cautiously because the site of action of the K^+ channel blockers was not

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established; vascular SMCs, endothelial, neural or parenchymal BK_{Ca} channels could have been affected. In rat spinotrapezeus muscle, *in vivo*, both TEA and iberiotoxin produce arteriolar constriction (951), consistent with a negative feedback role in the regulation of myogenic tone. Similarly, TEA has been shown to increase human forearm vascular resistance supporting a role for BK_{Ca} channels in resting vascular tone in this vascular bed (1123). However, in another study using the same protocol, TEA did not significantly increase forearm vascular resistance in healthy individuals (1122). Rat basilar arteries, *in vivo*, constrict when exposed to 10 mmol/L TEA suggesting that BK_{Ca} channels contribute to resting membrane potential and tone in these arteries, although a role for TEA-sensitive K_V channels cannot be excluded due to the high concentration of TEA used in this study (445). Other investigators have shown that a lower concentration of TEA (1 mmol/L) reduced rat basilar artery diameter by only 5% (1140), 10% (1316), or 13% (404). In this same model, iberiotoxin either had a small effect [5% constriction (1140)], or no significant effect (404). Taken together, these data suggest a small role for BK_{Ca} channels in determining the resting myogenic tone of basilar arteries in the rat, *in vivo*. Iberiotoxin has also been shown to depolarize SMC membrane potential in rat mesenteric resistance arteries, *in vivo* (778), consistent with a role for BK_{Ca} channels in the negative feedback regulation of myogenic tone in this vessel.

Evidence against BK_{Ca} channels in the negative-feedback regulation of myogenic tone—In contrast to the reports cited earlier, a number of studies have failed to implicate BK_{Ca} channels in the regulation of resting membrane potential and tone, particularly in arterioles. Perforated patch (673) or conventional whole-cell (665) recording of K^+ currents in second-order rat and hamster cremasteric arteriolar muscle cells have failed to find any effect of iberiotoxin on currents at physiological membrane potentials (−90 to 0 mV), even when cells are dialyzed with solutions containing 300 nmol/L free Ca^{2+} (665). Currents inhibited by iberiotoxin could be detected at positive membrane potentials in these studies (665). Consistent with these findings, iberiotoxin has no significant effect on resting membrane potential of single cremasteric arteriolar muscle cells (673). These data suggest that BK_{Ca} channels do not contribute to resting membrane potential in relaxed SMCs from these arterioles or even when cytosolic Ca^{2+} is raised to 300 nmol/L. This hypothesis is supported by *in vivo* studies demonstrating that neither iberiotoxin nor TEA affect resting diameter of hamster (672, 1532), rat (898), or mouse (1303) cremasteric arterioles *in vivo*, despite these vessels having substantial resting, myogenic tone. We have observed similar results in the hamster cheek pouch preparation: TEA (1 mmol/L, selective for BK_{Ca} channels) has no effect on resting diameter of second-order arterioles in this preparation (Jackson, unpublished observations). Similarly, iberiotoxin, TEA or charybdotoxin do not affect resting diameter of rat pial arterioles, *in vivo*, despite significant resting myogenic tone (617, 816, 969, 1139, 1141, 1319, 1320, 1489). Identical results were reported in cats (1511) and newborn pigs (58, 59). In rabbits, 50 nmol/L iberiotoxin had no effect on resting pial arteriolar diameter, whereas 100 nmol/L produced only a 3% constriction (1371). In fawn hooded rats, administration of penetrem A or iberiotoxin into eyes results in no significant change in retinal arteriolar diameter, although both produced a 10% decrease in arteriolar blood flow, which was computed from the vessel diameter and red blood cell velocity suggesting upstream effects (1066). Other investigators have previously reported no

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effect of iberiotoxin on resting retinal arteriolar diameter in Wistar rats (1030). Iberiotoxin has little effect on renal microvessels, *in vivo* (929). A lack of effect of TEA on resting blood flow to feline hind limb has also been reported (220). In addition, there are a few *in vitro* studies where BK_{Ca} channel blockers have little or no effect on pressure-induced arteriolar tone. Neither iberiotoxin nor TEA significantly affects resting diameter of isolated-cannulated porcine retinal arterioles (1044, 1385), Iberiotoxin has little effect on the diameter of pressurized rat cerebral parenchymal arterioles, (257, 301). First-order hamster cremaster arterioles studied by pressure myography constrict when superfused with charybdotoxin (10% constriction) or TEA (1 mmol/L; 19% constriction), but not iberiotoxin (3% constriction) (1596). Iberiotoxin was reported to have no effect on resting diameter of rat gracilis feed arteries, studied by pressure myography, *in vitro*, whereas charybdotoxin, which also inhibits endothelial IK_{Ca} channels, and a high concentration (10 mmol/L TEA) caused constriction (1446). In contrast, in studies by Samora et al. (1248) iberiotoxin was found to significantly constrict isolated rat gracilis feed arteries. TEA (1 mmol/L) reportedly has no significant effect on the diameter of cannulated coronary arterioles isolated from Yucatan minipigs (577). Iberiotoxin enhanced myogenic tone at low pressures in first-order arterioles from soleus muscle isolated from aged rats, but had no effect on myogenic tone of these same vessels isolated from young rats (730).

BK_{Ca} channel Ca^{2+} setpoint and the negative-feedback regulation of myogenic tone—Thus, the role played by vascular SMC BK_{Ca} channels on resting myogenic tone in systemic microvascular beds remains unclear. The lack of apparent activity of BK_{Ca} channels in some systems could be due to a lack or low expression of the channels; low voltage sensitivity (reduced slope of the voltage activation relationship); low Ca^{2+} sensitivity (reduced slope of the Ca^{2+}-activation relationship); a high Ca^{2+} setpoint (Ca^{2+} threshold for voltage-dependent activation) of the channels expressed; differences in the source and magnitude of Ca^{2+} signals that activate these channels; or differences in membrane potential (672). In SMCs isolated from hamster second-order cremaster arterioles, a high Ca^{2+} setpoint appears to contribute to the lack of activity of BK_{Ca} channels in these cells (672). In this model, as noted earlier, no activity of BK_{Ca} channels was observed in relaxed resting cells studied by the perforated patch technique (673), in cells dialyzed with up to 300 nmol/L Ca^{2+} (665), or inferred from functional studies of arterioles under resting conditions, *in vivo* (672). This lack of activity of BK_{Ca} channels was not due to the absence of these channels as a normal, relatively high density (1–8 channels in essentially every patch) of high conductance (242 pS in symmetrical 140 mmol/L K^+), iberiotoxin-sensitive channels were observed in inside-out patches of membrane from these cells (672). Furthermore, the voltage (16 mV per e-fold change in activity) and Ca^{2+} (85 mV/ten-fold change in Ca^{2+} concentration) sensitivities of the channels were similar to what had been reported in other SMCs (672). What appeared to be responsible for the low BK_{Ca} channel activity was a relatively high (9 μmol/L) Ca^{2+} setpoint (672). This value represents the concentration of Ca^{2+} required for activation of the channels to 50% of maximum at 0 mV (198, 672) and is an index of the threshold of Ca^{2+} required for physiological activation of the channels. In vascular SMCs isolated from larger arteries and other SMCs, the Ca^{2+} setpoint is on the order of 1 μmol/L (29, 111, 198, 646, 981); values that are 6- to 18-fold lower than the setpoint measured in hamster cremaster arteriolar muscle cells (672). Put in more

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physiological terms, the high Ca^{2+} setpoint in cremasteric arteriolar muscle cells means that the internal face of the membrane of these cells must be exposed to Ca^{2+} concentrations on the order of 3 μM for any activity of the channels to be observed at negative membrane potentials (665, 672). A high Ca^{2+} setpoint (~12 μmol/L) has also been measured in SMCs isolated from rat first-order cremaster arterioles (1593), and appears to arise from reduced expression of β1 subunits in these arteriolar SMCs relative to cerebral arteries (1589, 1593) and possible differences in expression of spliced variants (1098). It was also shown that siRNA knockdown of β1 subunit expression in SMCs isolated from cerebral arteries produced a phenotype (increased Ca^{2+} setpoint) similar to what was observed in cremaster arteriolar SMCs (1593). These data are consistent with data from heterologous expression systems where expression of BK_{Ca} channel α subunits alone yields channels with a Ca^{2+} setpoint on the order of 30 μmol/L, whereas expression of both α and β1 subunits produces channels with a Ca^{2+} setpoint on the order of 5 μmol/L [estimated from data in (974)]. Differences in coupling of α and β1 subunits, or differences in β1 expression were proposed to explain the heterogeneity of activity of BK_{Ca} channels in vascular muscle cells isolated from human coronary arteries (1382). Consistent with the hypothesis that there are regional differences in β1 subunit expression, SMCs from second-order mouse cremaster arterioles express only 55% of the β1 subunit expressed in SMCs isolated from upstream feed arteries (Jackson, unpublished observations). Thus, a high Ca^{2+} setpoint due to reduced β1 subunit expression in the SMCs in arterioles may account for some of the apparent lack of activity of these channels under resting conditions. However, this high Ca^{2+} setpoint cannot explain why BK_{Ca} channels are silent in arterioles studied *in vivo* [see, e.g., (672)], yet are active in the same vessels when studied, *in vitro* [see, e.g., (1528)]. Instead, it is proposed that the source of activator Ca^{2+} for BK_{Ca} channels accounts for the differences observed *in vivo* versus study of the same vessels, *in vitro*.

Sources of activator Ca^{2+} for BK_{Ca} channels

The source of Ca^{2+} that controls the activity of BK_{Ca} channels in resistance arteries and arterioles appears to display regional differences. Studies in cerebral arteries have shown that BK_{Ca} channels in isolated cells and in vessels studied, *in vitro*, using pressure myography, are controlled largely through Ca^{2+} released from RyRs in the form of Ca^{2+} sparks (Fig. 4) (176, 483, 682–684, 765, 1072, 1075, 1154, 1155, 1170, 1518, 1519), and similar results have been obtained in SMCs from coronary arteries (189, 453).

Benham and Bolton (110) were the first to describe spontaneous transient outward currents (STOCs), bursts of activity of BK_{Ca} channels in SMCs isolated from rabbit ear arteries and jejunum that arose from cyclical release of Ca^{2+} from internal stores. However, they did not establish a physiological function for these events. Subsequently, STOCs were identified in many vascular SMC preparations including, but not limited to: rabbit portal vein (104), hog carotid artery (329), guinea pig coronary artery (458), porcine coronary arteries (1333), rat basilar arteries (1338), human mesenteric arteries (1311), bovine coronary arteries (1334), rat cerebral arteries (1071), rat aorta (888), human coronary arteries (484), guinea pig mesenteric and submucosal arterioles (598), rat hepatic arteries (1660), canine renal arteries (663), rat renal arteries (131), mouse cerebral arteries (1168), rat mesenteric arteries (850), rat tail artery (243), porcine coronary arterioles (1020), guinea pig mesenteric arteries

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(1178), rat coronary arteries (264), rabbit basilar artery (1132), rat saphenous arteries (428), rat cremaster first-order arterioles (1589), and mouse superior epigastric arteries (573).

Early studies showed that STOCs were inhibited by ryanodine in SMCs from rabbit portal vein (782), but this was interpreted as a result of depletion of internal stores, not a specific role for RyRs in these events. However, subsequent studies by Nelson and colleagues (1071) identified Ca^{2+} sparks through RyRs as the source of Ca^{2+} the controls BK_{Ca} channel activity underlying STOCs. More importantly, they found that inhibition of RyR function with ryanodine, or inhibition of BK_{Ca} channel activity with TEA or iberiotoxin caused equivalent constriction of pressurized rat cerebral arteries, and that prior application of either ryanodine or one of the BK_{Ca} channel blockers eliminated subsequent effects of application of the other blocker. These data implied that BK_{Ca} channel activity in an intact, myogenically active artery was controlled by the activity of RyRs in the form of Ca^{2+} sparks and that this mechanism operates to provide an important negative feedback signal to limit myogenic tone.

While many studies have confirmed a role for RyR-based Ca^{2+} sparks in the control of BK_{Ca} channel activity, not all vessels use this mechanism. *In vitro* studies of second-order hamster (1528) and mouse (1527) cremaster arterioles have failed to detect Ca^{2+} sparks, and ryanodine is without effect on myogenic tone in these vessels. This did not appear to be methodological, because Ca^{2+} sparks were detected in upstream cremaster feed arteries, and ryanodine abolished these events and produced the expected vasoconstriction using identical methods (1527, 1528). In the arterioles, BK_{Ca} channels were active and contributed to the negative feedback control of myogenic tone (1527, 1528). However, it appeared that the source of Ca^{2+} controlling these channels originated from Ca^{2+} influx through L-type VGCCs, rather than from RyR-based Ca^{2+} sparks (1527, 1528) (Fig. 4). Studies in neurons (120, 508, 1355), in SMCs from rabbit coronary arteries (514) and in SMCs from mouse mesenteric arteries (1364) have shown that Ca^{2+} influx through L-type VGCCs can directly activate BK_{Ca} channels, supporting this idea. BK_{Ca} channels, L-type VGCCs and caveolin-1 colocalize in rat mesenteric vascular SMCs where tight coupling between BK_{Ca} channels and L-type Ca^{2+} channels has been demonstrated (1364). It should be noted that in contrast to the findings in rat cerebral arteries where BK_{Ca} channels appear to be solely controlled by RyR-based Ca^{2+} sparks (1071), in hamster (1528) and mouse (1527) cremaster feed arteries, Ca^{2+} influx, in addition to RyR-based Ca^{2+} sparks, contributes to the control of BK_{Ca} channel activity. Thus, there may be a spectrum of phenotypes for control of BK_{Ca} channel activity from solely RyR-based Ca^{2+} sparks to solely Ca^{2+}-influx through L-type VGCCs.

We think that control of BK_{Ca} channels by VGCCs in cremaster arterioles explains why BK_{Ca} channels appear silent at rest, *in vivo*, but contribute to the negative-feedback regulation of myogenic tone when these same vessels are studied, *in vitro*, by pressure myography. *In vivo*, myogenic tone of second-order cremaster arterioles appears resistant to L-type Ca^{2+} channel blockers (599, 670). In contrast, blockade of L-type VGCCs produces substantial dilation of these vessels when they are studied, *in vitro* (185). Thus, *in vivo*, at rest when L-type VGCCs are silent, BK_{Ca} channels are silent (672). In contrast, *in vitro*, where pressure-induced myogenic tone depends on Ca^{2+}-influx through L-type-VGCCs, BK_{Ca} channels are active and contribute to the negative-feedback control of myogenic tone

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(1527, 1528). Note that *in vivo*, induction of agonist or oxygen-induced tone, which depends on Ca^{2+}-influx through L-type VGCCs, activates BK_{Ca} channels that limit the vasoconstriction (672).

Coupling of Ca^{2+}-influx through VGCCs to the activity of BK_{Ca} channels does not appear to explain the lack or low activity of BK_{Ca} channels in cerebral penetrating arterioles. Instead, RyR-based Ca^{2+} sparks appear to be absent under resting conditions, limiting the activity of the BK_{Ca} channels (301). However, exposure of SMCs to acidic solutions activates the RyRs, generating Ca^{2+} sparks which then activate BK_{Ca} channels to contribute to vasodilation during acidosis. These data further support the idea that there are regional differences in the mechanisms controlling BK_{Ca} channel function.

Vasoconstrictors and BK_{Ca} channels

Vasoconstrictor-mediated inhibition of BK_{Ca} channels—Calcium-activated K^+ channels have been reported to play both a positive (817, 1272, 1417, 1526) and negative (116, 175, 458, 566, 672, 1071, 1074, 1228, 1486) feedback role in the mechanism of action of vasoconstrictors. As with K_V channels (earlier) and K_{ATP} channels (later), activation of PKC, a common step in the mechanism of action of many vasoconstrictors (620, 836), appears to inhibit BK_{Ca} channels in some vascular SMCs (817, 1004) and in other systems (1201, 1631) (Fig. 6). The functional significance of this inhibition has not been well studied. However, in small mesenteric arteries, blockade of BK_{Ca} channels with charybdotoxin, TEA or iberiotoxin inhibits pressure-induced depolarization and myogenic reactivity (1526) suggesting that closure of BK_{Ca} channels plays a role in pressure-induced vasoconstriction in some systemic arteries. In addition, the vasoconstrictor angiotensin II has been shown to cause internalization and degradation of BK_{Ca} channels in a PKC-dependent fashion, providing an additional mechanism to contribute to vasoconstriction induced by this vasoactive agent (843).

Vasoconstrictor-mediated activation of BK_{Ca} channels—Despite the evidence presented earlier, other studies suggest that BK_{Ca} channels play a negative feedback role in the mechanism of action of vasoconstrictors including elevated intravascular pressure. In a number of systems, inhibition of BK_{Ca} channels augments the effects of vasoconstrictors (220, 672, 1487, 1526) in the absence of effects on basal tone (Fig. 6). For example, in hamster cremasteric arteriolar SMCs, iberiotoxin increases the response of single cells to norepinephrine (672). Contraction of these SMCs by norepinephrine is correlated with a large, reversible increase in the opening of single BK_{Ca} channels in cell attached patches that can be inhibited by inclusion of 1 mmol/L TEA in the pipette solution (667). Vasopressin (1486), endothelin-1 (1244) and histamine (566) have also been reported to increase BK_{Ca} channel activity in vascular SMCs. Arteriolar vasoconstriction induced by elevated PO_2 in hamster cremaster muscle is enhanced by TEA, suggesting that BK_{Ca} channels are activated during this process (672). In porcine coronary arteries, IP_3 has been proposed to directly activate BK_{Ca} channels, contributing to the negative-feedback regulation of vasoconstrictor-induced SMC tone (1582). Thus, vasoconstriction appears to be associated with an increase in BK_{Ca} channel activity, rather than a decrease as predicted from the studies mentioned above. In addition, pressure-induced activation of BK_{Ca} channels has been reported in

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several systems (116, 175, 1071). It may be that while activation of PKC might cause some channel inhibition, the increase in intracellular Ca^{2+} as well as the membrane depolarization induced by vasoconstrictors, remain sufficient to activate enough BK_{Ca} channels to limit the degree of membrane depolarization that occurs. Future studies in which membrane potential, subsarcolemmal calcium, BK_{Ca} channel activity and vascular SMC tone are measured simultaneously during application of vasoconstrictors, or elevated pressure will be required to test this hypothesis.

Vasodilators and BK_{Ca} channels

cAMP signaling and BK_{Ca} channels—The role played by BK_{Ca} channels in the mechanism of action of vasodilators remains controversial. Sadoshima et al. (1230) first demonstrated that cAMP-mediated activation of PKA activates BK_{Ca} channels in patch clamp studies of cultured rat aortic SMCs. Subsequent studies in other systems have confirmed and extended these results (799, 801) (Fig. 6). Phosphorylation of the BK_{Ca} α-subunit at serine 869 appears to be involved in effects of PKA on BK_{Ca} channel activity (1053, 1410, 1411). These K^+ channels may also be activated by the guanine nucleotide binding protein, $G\alpha_s$, independent from cAMP and PKA (799, 800, 1271). Vasodilators that act via cAMP, such as isoproterenol, may also activate BK_{Ca} channels by increasing subsarcolemmal Ca^{2+} concentrations (1572) and the frequency of Ca^{2+} sparks (1169). This latter effect may involve cAMP-mediated, PKA-dependent phosphorylation of phospholamban and the resultant increase in SERCA activity, which elevates store Ca^{2+} load (1521). Finally, dilators that act via cyclic nucleotides can also increase the trafficking of β1 subunits to the plasma membrane, dynamically increasing the association of these accessory proteins with the α-subunits, increasing the Ca^{2+} sensitivity of the BK_{Ca} channels (961). In aortic SMCs, β_2-adrenergic receptors associate with BK_{Ca} channels in complexes with AKAP150 and Ca_V 1.2 VGCCs suggesting an intimate relationship between a $G\alpha_s$-coupled receptor and BK_{Ca} channels (891). All of the aforementioned studies suggest that vasodilators, such as isoproterenol, prostacyclin, adenosine, CGRP, etc., which bind to receptors coupled to adenylate cyclase via $G\alpha_s$-proteins, may relax vascular SMCs, at least in part, by activation of BK_{Ca} channels and membrane hyperpolarization.

Agonists that activate adenylate cyclase to increase the production of cAMP also may activate BK_{Ca} channels via exchange proteins activated by cAMP [EPACs (480)] as has been demonstrated in rat mesenteric artery (1206) (Fig. 6). In this model, a selective agonist of EPACs, 8-pCPT-2'-O-Me-cAMP, increased the frequency of Ca^{2+} sparks and BK_{Ca}-associated STOCs, resulting in SMC cell membrane hyperpolarization and relaxation (1206). In addition to the effects of the EPAC agonist on Ca^{2+} spark and STOC frequency, Roberts et al. (1206) found that the amplitude of STOCs was increased, despite no change in the amplitude of Ca^{2+} sparks. These data suggest that EPACs may mediate effects on RYRs (resulting in the increase in spark and STOC frequency) and directly on BK_{Ca} channels (resulting in the increase in STOC amplitude).

The hypothesis that BK_{Ca} channels mediate at least a portion of the dilator response of blood vessels to cAMP-related vasodilators is supported by many, but not all, functional studies of isolated blood vessels. Dilation or relaxation induced by the adenylate cyclase activator,

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forskolin (90, 961, 1110, 1169, 1371); the cell-permeant cAMP analog, dibutyryl cAMP (1139, 1383); or receptor-mediated agonists such as adenosine (191, 201, 1139); di-adenosine poly phosphate (1354); CGRP (617); isoproterenol (961, 1254); iloprost (1270); prostacyclin (60); PGE_2 (60); vasoactive intestinal polypeptide (VIP) (1383); adenylate-cyclase-activating peptides (178); and 11,12-EET (642) are all inhibited by iberiotoxin, charybdotoxin and/or TEA (1 mmol/L).

In contrast, dilation of the vasculature in cat hind limb induced by albuterol and prostaglandin E1, which should be mediated by cAMP, are not affected by blockade of BK_{Ca} channels with TEA (220). Systemic dilation induced by adenosine is only slightly attenuated by infusion of iberiotoxin in anesthetized pigs (1619). Relaxation of rat aorta by dibutyryl cAMP is not inhibited by iberiotoxin (1254). Adenosine-induced dilation of pig coronary arterioles is not inhibited by iberiotoxin (580). Forskolin-induced dilation of the renal vascular bed is not inhibited by iberiotoxin (929). In contrast to previous studies utilizing iberiotoxin (1139), adenosine-induced dilation of rat pial arterioles was not inhibited by an effective concentration of paxilline (1125). Dilation of porcine coronary arteries to PGE_2 is not inhibited by iberiotoxin (1403). These data suggest that there may be regional or species differences in the role played by BK_{Ca} channels in cAMP-related vasodilation or that subtle methodological differences can alter the role played by these channels.

NO-cGMP-PKG-signaling and BK_{Ca} channels—Vasodilators that signal through the cGMP-PKG pathway, such as the nitrovasodilators and endogenous NO, also activate BK_{Ca} channels (Fig. 6). Early studies showed that SMC relaxation induced by the NO-donor, SNP or atrial natriuretic peptide (which activates particulate guanylate cyclase to produce cGMP) were impaired in rabbit aorta contracted with 80 mmol/L K^+ (1539), consistent with a role for K^+ channels in the mechanism of action of these cGMP-related vasodilators, and 10 mmol/L TEA inhibited relaxation of rabbit aorta to natriuretic peptide (1538). Subsequent patch clamp studies demonstrated that SNP, atrial natriuretic peptide, or dibutyryl cGMP increased the open-state probability of BK_{Ca} channels in cell-attached patches of cultured bovine aortic SMCs (1533). However, the authors concluded that it was cGMP that activated the channels directly, rather than an effect mediated via cGMP-dependent activation of PKG. Nitroglycerin and 8-Br-cGMP were then shown to increase BK_{Ca} channel activity in cell-attached patches of primary cultured SMCs from porcine coronary arteries (446). Subsequently, the NO-donor, SIN-1, and the membrane permeant analog of cGMP, 8(4-chlorophenylthio)-cGMP, were shown to activate BK_{Ca} channels in cell-attached patches of rabbit basilar artery SMCs (1209). Importantly, Robertson et al. (1209) were the first to show that PKG specifically activated BK_{Ca} channels in inside-out patches of rabbit basilar artery SMCs. This was confirmed in membrane patches from canine coronary SMCs (1388). Taniguchi et al. (1388) also reported that charybdotoxin inhibited relaxation induced by atrial natriuretic peptide, consistent with a role for cGMP/PKG activation of BK_{Ca} channels. The NO-donor, NONOate increased the activity of BK_{Ca} channels in cell-attached patches of bovine coronary artery SMCs (867). In addition, NO modulates the frequency of Ca^{2+} sparks affecting the activity of BK_{Ca} channels (699, 938, 1613). In contrast, endothelium-derived NO inhibits the relaxation of the porcine coronary artery to natriuretic peptides by desensitizing BK_{Ca} channels (870).

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Consistent with the electrophysiological results outlined earlier, studies in rabbit superior mesenteric arteries (743), horse penile arteries (1307), rat coronary arteries (1174, 1517), rat mesenteric arteries (1162), rat pial arterioles, *in vivo*, (1139), canine middle cerebral arteries (1108, 1109), human coronary arteries (190), rat middle cerebral arteries (1356) indicate that blockade of BK_{Ca} channels inhibits relaxation or dilation of these vessels. In addition, insulin-induced increases in human skin blood flow are mediated by NO and BK_{Ca} channels (472). These data all support a role for BK_{Ca} channels in the mechanism of action of NO on vascular SMCs.

Supporting a role for phosphorylation in NO-mediated activation of BK_{Ca} channels, phosphatase inhibition potentiated cGMP-dependent activation of pulmonary artery SMC BK_{Ca} channels (54). Phosphorylation of the α subunit of BK_{Ca} channels by PKG, *in vitro*, was reported in channels isolated from tracheal SMCs (34), human BK_{Ca} channels expressed in Xenopus oocytes (35), and murine BK_{Ca} channels (1366). Site-directed mutagenesis identified serine 1072 as an essential PKG phosphorylation site in studies of human embryonic kidney (HEK) cells expressing BK_{Ca} channels cloned from canine colonic SMCs (cSlo) (450). In contrast, site-directed mutagenesis indicated that PKG-dependent phosphorylation at serines 855 and 869 are required for full activation of BK_{Ca} channels in Xenopus oocytes stimulated with NO or atrial natriuretic peptide and expressing hSlo and $h\beta_1$ (1052). Expression of a kinase-dead mutant of PKG eliminates effects of NO donors and cGMP analogs on murine BK_{Ca} channels expressed in HEK cells supporting a role for PKG-dependent phosphorylation (1366). Phosphopeptide and phophoamino acid mapping and site directed mutagenesis of murine BK_{Ca} channels have identified serine 873 and serines 1111–1113 [serine 1112 is equivalent to serine 1072 reported by (450)] as essential sites for PKG-mediated channel phosphorylation and cGMP/PKG-dependent modulation of BK_{Ca} channel function (807). However, in mesangial cells and an HEK cell expression system, dibutyryl cGMP-induced activation of BK_{Ca} channels depended on the presence of the β_1 subunit (794). Furthermore, in rat cerebral vascular myocytes, NO, via activation of PKG, stimulates anterograde trafficking of β_1 subunit to the plasma membrane, association with BK_{Ca} α subunits, and subsequent activation of BK_{Ca} channels which contributes to NO-mediated vasodilation in these vessels (842).

Nitric oxide also appears to have the potential to activate BK_{Ca} channels independent from cGMP. Bolotina et al. (151) showed that NO could activate these channels in inside-out patches of rabbit aortic SMC cell membranes and that charybdotoxin inhibited NO-induced, cGMP-independent relaxation of the same tissue. Similarly, the NO-donor, SNP, increased the open-state probability of BK_{Ca} channels in cell-free patches of rat tail artery (1546) and rat middle cerebral arteries (1356), supporting this hypothesis. Activation of BK_{Ca} channels by NO, independent from cGMP/PKG also has been reported in other systems (16, 188, 814, 815). Charybdotoxin-sensitive dilation induced by the NO-donor, 3-morpholinosydnonimine (SIN-1) of rat mesenteric arteries (1162, 1164) and activation of BK_{Ca} channels in SMCs from these vessels (1011) also appears to occur independent of activation of guanylate cyclase. Studies in rat small mesenteric arteries also suggest that NO may activate BK_{Ca} channels in a cGMP-independent manner, although functional studies were not performed to demonstrate a role for this process in NO-induced vasodilation (1512). Inhibition of soluble guanylate cyclase inhibits, but does not abolish NO-induced activation of BK_{Ca} channels

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(854). Inhibition of guanylate cyclase does not inhibit charybdotoxin-sensitive relaxation of canine middle cerebral arteries (1109). Similarly, activation of BK_{Ca} channel currents in SMCs isolated from human radial arteries by an NO donor is resistant to inhibition of guanylate cyclase suggesting cGMP/PKG-independent effects (1630), consistent with a direct effect of NO on BK_{Ca} channels. These data also suggest that cGMP-dependent and independent mechanisms for NO-induced activation of BK_{Ca} channels may exist in the same cells. Nitric oxide-induced relaxation of human umbilical arteries is inhibited by iberiotoxin, but appears independent from cGMP (907). Dilation of rat middle cerebral arteries induced by DEA-NONOate is inhibited by iberiotoxin, whereas this BK_{Ca} channel blocker has little effect on dilation induced by 8-Br-cGMP (1608), suggesting cGMP-independent activation of BK_{Ca} channels in this model.

Despite the evidence presented earlier, other studies suggest no direct effect of NO on BK_{Ca} channels. Nitric oxide donors increase BK_{Ca} channel activity in cell-attached patches, but have no effect on BK_{Ca} channels in cell-free patches of membrane from cultured bovine aortic SMCs (1533). Similar results have been reported for heterologously expressed BK_{Ca} channels (450). NO-donor-induced activation of BK_{Ca} channels is absent in aortic SMCs isolated from PKG knockout mice (1255). Similarly, in an expression system, NO-donor induced activation of BK_{Ca} channels could be prevented by coexpression of a kinase-dead mutant of PKG (1366). Thus, the bulk of evidence suggests that NO and NO-donors activate BK_{Ca} channels through cGMP/PKG-dependent mechanisms.

In contrast to the studies supporting NO-induced activation of BK_{Ca} channels, there is also a body of evidence suggesting that the mechanism of action of NO does not involve the activation of these channels. Studies in feline hind limb have failed to demonstrate inhibition of nitrovasodilator-induced vasodilation with TEA, despite other effects consistent with effective blockade of BK_{Ca} channels (220). Other studies have also failed to demonstrate effects of BK_{Ca} channel blockade on NO-induced vasodilation (59, 136, 473, 1647) or relaxation of isolated vessels (136, 274, 337, 449, 551, 593, 747, 1165, 1371, 1516, 1647). In addition, NO does not hyperpolarize SMCs in rabbit middle cerebral arteries (174) or rabbit basilar arteries (1161). Nitric oxide hyperpolarizes SMCs in rat mesenteric arteries, but this hyperpolarization is inhibited by the K_{ATP} channel blocker, glibenclamide (465). Relaxation and hyperpolarization of rat superior mesenteric arteries to SNAP is not inhibited by charybdotoxin (473). Thus, as with cAMP-related vasodilators, there may be species or regional differences in the role played by BK_{Ca} channels in NO-induced vasodilation.

Other vasodilators and BK_{Ca} channels—In addition to endothelium-derived NO, other endothelium-derived vasodilators have also been proposed to act, in part, by activation of BK_{Ca} channels. Carbon monoxide produced endogenously from metabolism of heme groups by the heme oxygenases activates BK_{Ca} channels (7, 1494, 1495) (Fig. 6). In rat tail artery, vasodilation induced by CO is inhibited by charybdotoxin, but not by apamin (1494). These data are supported by studies showing a direct effect of CO on BK_{Ca} channel activity in inside-out patches of rat tail artery membranes (1494, 1495), independent from changes in cGMP, as CO also activates guanylate cyclase (746). BK_{Ca} channels bind heme proteins, which serve as the receptor for CO-dependent activation of these channels (680). Carbon monoxide also increases the frequency of Ca^{2+} sparks and increases the coupling of Ca^{2+}

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sparks to BK_{Ca} channels in cerebral SMCs (679), likely by increasing the Ca^{2+} sensitivity of the channels (1556). Glutamate-induced dilation of cerebral arterioles in brain slices of neonatal pigs involves astrocyte-derived CO, activation of guanylate cyclase, and increase in Ca^{2+} spark frequency and a reduction in global Ca^{2+} concentration in cerebral arteriolar SMCs (865, 1557).

Epoxyeicosatrienoic acids (EETs), which serve as endothelium-derived relaxing factors in some blood vessels, also have been shown to activate BK_{Ca} channels. In bovine coronary arteries EET-induced relaxation is inhibited by TEA (1 mmol/L) or charybdotoxin (194). These arachidonic acid (AA) metabolites also hyperpolarized SMCs in these vessels and increased the activity of BK_{Ca} channels in patch clamp experiments (194), providing evidence that EETs act, in part, by activation of BK_{Ca} channels. Similarly, relaxation and hyperpolarization of guinea pig coronary arteries induced by 11,12 EET is inhibited by iberiotoxin (370). Iberiotoxin also inhibits dilation and SMC hyperpolarization induced by endothelium-derived EETs in rat gracilis arteries (631). It appears that the effects of EETs on BK_{Ca} channels may be indirect as it has been proposed that EETs activate TRPV4 channels inducing Ca^{2+} influx, that stimulates RyR-mediated Ca^{2+} sparks, which, in turn, activate overlying BK_{Ca} channels (364).

There is also evidence that H_2O_2 and H_2S act through BK_{Ca} channels in some blood vessels. In porcine coronary artery SMCs, H_2O_2 activates BK_{Ca} channels (92), and H_2O_2-induced dilation of porcine coronary arteries is inhibited by iberiotoxin (1403) (Fig. 6). Tumor necrosis factor (TNF) α dilates cerebral resistance arteries, in part, by stimulation of Ca^{2+} sparks and activation of BK_{Ca} channels by a mechanism involving activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and production of H_2O_2 (242).

In cerebral arterioles isolated from newborn pigs, H_2S stimulates Ca^{2+} sparks which activate BK_{Ca} channels to hyperpolarize the SMCs and produce vasodilation (871). An indirect mechanism involving H_2S-induced Ca^{2+} spark stimulation of BK_{Ca} channels also has been proposed in rat mesenteric arteries (676).

Functional vasodilation and BK_{Ca} channels

Relatively few functional studies have been performed to determine the role played by BK_{Ca} channels in the regulation of blood flow in systemic vascular beds. Hyperosmolarity (319) and low extracellular pH (301, 877), two conditions that are associated with functional hyperemia in several organ systems, are mediated, in part, by activation of BK_{Ca} channels. Active hyperemia in canine diaphragm is partially inhibited by iberiotoxin, particularly at low levels of activity (1462). Similarly, BK_{Ca} channels modestly contribute to functional hyperemia in human forearm (1122). These data suggest that BK_{Ca} channels play at least a small role in the functional regulation of blood flow in skeletal muscle. However, the role played by BK_{Ca} channels in reactive hyperemia is unclear. In canine diaphragm, iberiotoxin inhibits a portion of the hyperemia induced by vascular occlusion (1463), supporting a role for BK_{Ca} channels in this response. Exercise training also has been shown to enhance BK_{Ca} channel function in mesenteric arteries through increases in the expression of the β1 subunit (1295). In contrast, studies in the cat hind limb found no effect of TEA on reactive

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hyperemia (220), suggesting no role for BK_{Ca} channels. Thus, there may be species-dependent differences in the contribution of BK_{Ca} channels to the hyperemia after vascular occlusion.

Reactive-hyperemia to 5 min vascular occlusion is inhibited by both TEA and charybdotoxin in isolated rat hearts (1302). Block of BK_{Ca} channels with TEA in the pig coronary circulation resulted in a decrease in resting vascular conductance and a decrease in exercise-induced hyperemia (996). These data suggest that in the BK_{Ca} channels may participate in reactive- and functional-hyperemia in the heart. Opposing this view are studies in the coronary circulation of Ossabaw pigs, using penitrem A to block BK_{Ca} channels that show no role for BK_{Ca} channels in resting coronary vascular resistance or in exercise-induced increases in blood flow in lean or obese pigs (158). Borbouse et al. (158) suggested that ganglionic blocking effects of TEA, rather than inhibition of BK_{Ca} channels might reconcile their study with that of Merkus et al. (996). Thus, the role played by BK_{Ca} channels in the local regulation of blood flow remains unclear.

Pathophysiology and BK_{Ca} channels

Hypertension—As with K_V channels discussed earlier, hypertension has been reported to both increase and decrease the expression and function of BK_{Ca} channels in resistance arteries and arterioles. A number of functional studies have shown that inhibition of BK_{Ca} channels causes contraction of vascular SMCs from hypertensive animals that is substantially larger than that observed in normotensive counterparts (65, 67, 890, 1140, 1227, 1228). This apparent increase in BK_{Ca} channel activity is associated with an increased BK_{Ca} channel current density in patch clamp experiments (890, 1227, 1228, 1628) and increased expression of BK_{Ca} channel proteins (890, 1228, 1628). This increased expression and function of BK_{Ca} channels may occur as a negative feedback response to the increased vascular reactivity observed in hypertension (1228).

In contrast, in Sprague-Dawley rats, angiotensin II-induced hypertension is associated with a decrease in BK_{Ca} channel function due to reduced Ca^{2+} sensitivity of BK_{Ca} channels resulting from decreased expression of the β1 subunit in cerebral arteries (39). Reduced expression of β1 subunits was also observed in vessels from SHR, but also in WKY rats with blood pressures that were intermediate between the Sprague-Dawley and SHR (43). Reduced function of BK_{Ca} channels correlated with reduced expression of β1 subunits also has been reported in aortic SMCs from SHR (860) and in human hypertension (1583). It was proposed that activation of NFATC3 resulted in the down regulation of the β1 subunits in angiotensin-induced hypertension (1082). BK_{Ca} channel function is also impaired in aortic SMCs from two-kidney: one-clip hypertensive rats (193).

In addition, BK_{Ca} channel currents are reduced with decreased expression of BK_{Ca} channel α subunits in mesenteric arteries from L-nitroarginine methyl ester-induced hypertensive rats (170, 171). In a mouse model of hypertension associated with increases in aldosterone, coronary artery dysfunction involves downregulation of expression and function of SMC BK_{Ca} channels (45). There also is decreased expression of BK_{Ca} channel α and β1 subunits in mesenteric artery SMCs from BPH versus BPN mice and a corresponding decrease in functional activity of BK_{Ca} channels in patch clamp studies (1028). The reason for these

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differences in BK_{Ca} channel expression and function is not known, but may relate to methodological differences, heterogeneity in the expression, function and regulation of BK_{Ca} channels in different vascular beds as well as strain- or species-dependent differences.

Obesity and the metabolic syndrome—The effects of obesity, hypercholesteremia, and the metabolic syndrome on BK_{Ca} channel expression and function is complex (1226). In obese pigs displaying the metabolic syndrome, the expression of BK_{Ca} channels is increased; however, their function is severely depressed relative to their lean counterparts (157, 158). Similarly, there is decreased BK_{Ca} channel function in SMCs from obese Zucker rats (440). Hypercholesterolemia also impairs BK_{Ca} channel function in porcine coronary artery SMCs (1581) and it has been shown that hypercholesterolemia impairs the function of BK_{Ca} channels in human forearm circulation (1123). In a mouse model of type 2 diabetes, BK_{Ca} channel function is depressed in both cerebral and mesenteric arteries due to decreased expression of β1 subunits (1099). Hyperglycemia was associated with activation of the transcription factor NFATC3 via calcineurin that is targeted to the appropriate cellular compartment by AKAP150 (1099). That hyperglycemia, alone, can induce this phenotype suggests that this mechanism may also be active in type 1 diabetes.

Aging—Aging impairs BK_{Ca} channel expression and function in coronary arteries of rats that can be partially restored by low intensity exercise training (27). In rat skeletal muscle feed arteries, advanced age reduces expression of BK_{Ca} channel subunits. However, their function in the regulation of myogenic tone appears to be increased in soleus arteries, but not affected in gracilis muscle arteries (730). There is decreased function and expression of BK_{Ca} channels in coronary arteries from Fisher 344 rats (942). Decreased expression was also reported in coronary arteries from aged humans (942). Aging also is associated with decreased expression of the β1 subunit that contributes to the age-related decrease in channel function (1094). In contrast, advanced age increases the amplitude of STOCs in SMCs from murine superior epigastric arteries (573) with no change in the expression of BK_{Ca} channels. However, despite the increase in STOC amplitude, the integrated function of these channels in the regulation of myogenic tone was similar in vessels from young (3–6 mo) and old (>22 mo) mice (573). Thus, the effects of aging on BK_{Ca} channel expression and function appear to be complex, and likely display regional variation.

Diabetes—The expression and function of BK_{Ca} channels appears to be reduced in type 1 diabetes (421, 884). It has been proposed that this may involve hyperglycemia-induced oxidative stress and the formation of peroxynitrite (884). In high fat/high cholesterol-fed pigs treated with alloxan to induce diabetes, there is a reduction in baseline coronary blood flow, enhanced constriction induced by $PGF_{2\alpha}$ and impaired adenosine-mediated dilation (1020). These functional changes were associated with a reduction in Ca^{2+} sparks and BK_{Ca} channel-mediated STOCs in SMCs isolated from coronary arteries from these animals, suggesting impairment of Ca^{2+} signaling and BK_{Ca} channel function (1020). Moderate exercise training prevented the changes that were observed except for the impaired vasodilator reactivity. Arachidonic acid–induced dilation of rat coronary arteries, which involves BK_{Ca} channels, is impaired in streptozotocin-induced diabetes (1645). Chronic (but not acute) treatment with a PKCβ inhibitor or with superoxide-dismutase restores AA-

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induced dilation implicating a role for ROS in the downregulation of BK_{Ca} channel function in this model system (1645). Streptozotocin-induced diabetes impairs BK_{Ca} channel function in SMCs from rat retinal arterioles due to decreased expression of β1 subunits (975). Similarly, in cerebrovascular SMCs, BK_{Ca} channel function is depressed in diabetes (338, 1497) due to increased ROS (338) and decreased expression of β1 subunit (1497). These data indicate that BK_{Ca} channel expression and function are depressed in diabetes and that this may contribute to the increased vascular tone and vasoconstrictor reactivity observed in this disease state (421, 884).

In contrast, diabetic dyslipidemia in alloxan-treated Yucatan mini-pigs resulted in increased vasoconstrictor reactivity of coronary arteries studied *in vivo* and *in vitro* (1021). However, whole-cell K^+ current densities, and caffeine-induced BK_{Ca} channel current densities were elevated, changes that were reduced by endurance exercise (1021). It was observed that STOC frequency was either decreased or remained the same relative to events in SMCs from untreated pigs, with no change in BK_{Ca} α subunit expression as assessed by Western blot. The increased K^+ current density may be compensatory to increased Ca^{2+} signaling. Disparate results between this study and others in the literature (see earlier) could be due to species differences, vessel heterogeneity and/or the duration or magnitude of the diabetic dyslipidemia.

Other disease states—Alcohol-induced cerebral vasoconstriction is mediated by closure of BK_{Ca} channels (893). Depletion of membrane cholesterol with methyl-β-cyclodextrin abolished this effect, which appeared to be mediated by interactions of cholesterol with the β_1 subunit (183).

In mice, heart failure induced by myocardial infarction results in increased myogenic tone in mesenteric resistance arteries due to decreased expression of both the α and β1 subunits of BK_{Ca} channels, reduced BK_{Ca} channel function, and membrane depolarization (1488). However, the mechanism for this BK_{Ca} channel remodeling was not established.

BK_{Ca} channels may also be involved in the decreased vascular reactivity observed in sepsis. In LPS or TNF-alpha-induced shock in mice, block of BK_{Ca} channels reduces mortality if SK_{Ca} channels also are blocked (213). This observation suggests an interplay between K^+ channel signaling in the endothelium with that in vascular SMCs.

K_{IR} Channels

Discovery of K_{IR} channels

Inward-rectifier K^+ channels derive their name from the fact that at membrane potentials negative to the K^+ equilibrium potential, these channels conduct K^+ ions into cells, whereas at more positive potentials, outward K^+ current is limited (594, 791, 1080, 1187). Inward rectification of membrane K^+ currents was first described by Katz in skeletal muscle (737). Subsequently seven families of 15 genes in the potassium channel family J (KCNJ) have been identified that encode K^+ channels which display inward rectification (791). This section will focus on the KCNJ family members that encode strong inward rectifiers, particularly KNCJ2 (K_{IR} 2.1) and KCNJ12 (K_{IR} 2.2) as these channels are highly expressed

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in vascular SMCs of resistance arteries and arterioles and determine the inward rectification of K^+ currents through SMC membranes (168, 689, 1313, 1621) as discussed below.

Structure of K_{IR} channels

Inward-rectifier K^+ (K_{IR}) channels are composed of a tetramer of pore-forming α subunits (594, 1080). Each α subunit has two membrane spanning domains (M1 and M2, Fig. 2) with intracellular carboxy and amino termini (594, 1080). The membrane spanning domains are linked by a P-loop that, along with M2, forms the ion-conducting pore and contains the K^+ ion selectivity filter of a K_{IR} channel (594, 1080). The characteristic inward rectification of K^+ current through K_{IR} channels occurs due to block of outward K^+ currents by intracellular polyamines (396, 424, 904) and Mg^{2+} (960, 1461) [see (908) for a review of this topic]. These positively charge moieties interact with negatively charged amino acids in M2 (D171 in K_{IR} 2.1) and in the carboxy terminal domains (E224 and E299 in K_{IR} 2.1) to block efflux of K^+ ions at membrane potentials positive to the K^+ equilibrium potential (908). In addition, and important for the physiological function of these channels, the conductance of K_{IR} channels increases in proportion to the square-root of the extracellular K^+ concentration (534, 792, 905, 936, 1235). This results from the presence of two K^+-binding sites in the P-Loop K^+ selectivity filter (594). Also important is the outward “hump” in the current-voltage relationship [i.e., a region of negative slope conductance (372, 1235)] that is observed at potentials positive to the K^+ equilibrium potential but negative to the resting membrane potential of most vascular SMCs of resistance arteries and arterioles (~−30 mV) (185, 380). Hyperpolarization of the membrane from the resting potential will activate K_{IR} channels and amplify the initial hyperpolarization (185, 668, 689, 903, 1313). Also, small increases in extracellular K^+ concentration will shift this region of negative slope conductance to more depolarized potentials (as the K^+ equilibrium potential shifts to more positive potentials), which, if this region encompasses the prevailing membrane potential, will lead to activation of outward current through the K_{IR} channels accounting for at least a part of the membrane hyperpolarization that is observed in vascular SMCs exposed to increases in extracellular K^+ up to about 20 mmol/L.

Modulation of K_{IR} channels by membrane lipids

Currents through K_{IR} 2 channels are strongly regulated by their lipid environment. Phosphatidylinositol 4,5-bisphosphate (PIP_2) activates K_{IR} 2 channels through interactions with positively charged residues in M2 and the cytoplasmic tails of the channels (594) opening the potential for modulation of K_{IR} channel function by PIP_2 hydrolysis and synthesis (594). Thus, agonists that act on $G_{q/11}$-coupled receptors could, potentially, inhibit K_{IR} channel function by stimulation of phospholipase Cβ and subsequent hydrolysis of PIP_2 to IP_3 and diacylglycerol. However, the affinity of K_{IR} 2.1 for PIP_2 binding is sufficiently high that local depletion of PIP_2 (by the action of phospholipases) does not strip these channels of activator PIP_2 (344). In contrast, K_{IR} 2.2 and 2.3 have lower PIP_2 affinity allowing stronger regulation by local hydrolysis of PIP_2 (344). Thus, it is possible that $G_{q/11}$-coupled receptor activity could modulate the function of K_{IR} 2.2 containing vascular K_{IR} channels, although this has not been adequately explored in SMCs from resistance arteries and arterioles.

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Membrane cholesterol also substantially impacts the function of K_{IR} channels, although the physiological significance of this has not been explored in vascular SMC K_{IR} channels. Increases in membrane cholesterol induced by exposure of cells to cholesterol-saturated methyl-β-cyclodextrin inhibits, while decreases in membrane cholesterol produced by methyl-β-cyclodextrin stimulates currents through K_{IR} 2 channels in endothelial cells (382, 400, 1215, 1217, 1218) and in heterologously expressed K_{IR} 2 channels (1214), with K_{IR} 2.1 and 2.2 being particularly sensitive to cholesterol manipulation (1214). Two cholesterol-binding domains have been identified: one in the hinge region of M1 and a second at the interface between M1 and the cytosolic domains (1217). This cholesterol sensitivity involves several amino acids (L222, N216, and K219) in the CD loop of the carboxy terminus of K_{IR} 2 channels that are also important for sensitivity to PIP_2 (382), and are part of a group of cytosolic residues that form a “cholesterol-sensitivity belt” around the putative pore of K_{IR} 2 channels affecting gating of the channels (1216). Studies of the bacterial K^+ channel K_{IR} Bac1.1 and K_{IR} 2.1 proteins incorporated into liposomes indicate that it is likely that cholesterol binds directly to the channel to modulate function (1308), through novel cholesterol binding motifs located near the hinge region of M1 and at the interface between M1 and the cytosolic domains (1217).

K_{IR} 2 channels preferentially partition into cholesterol-rich lipid rafts (1214). Removal of membrane cholesterol results in channel translocation out of these microdomains, whereas adding cholesterol has the opposite effect (1413). In addition to modulation of channel function by cholesterol, these channels also interact with caveolin-1, which also has a negative impact on K_{IR} channel function, stabilizing the channel in a closed state (548). The location of K_{IR} channels in caveolae positions them to potentially interact with and be modulated by a large number of other receptors, ion channels, protein kinases, etc. that assemble in these membrane signaling microdomains (139), similar to what has been described for K_{IR} 2 channels in cardiac myocytes (844, 1534). In heterologous expression systems, K_{IR} 2.1 has been shown to interact with AKAP79 that may help target PKA, calcineurin and other signaling proteins to these channels (307).

Evidence for K_{IR} channels in vascular SMCs

Edwards and Hirst were the first to describe vascular Ba^{2+}-sensitive inwardly rectified currents in guinea pig sub-mucosal (372) and rat cerebral (373) arterioles. However, because these currents were measured in intact arterioles, the cell-type conducting these currents could not be identified. Because SMCs are electrically coupled to endothelial cells (380, 1251) and endothelial cells also express K_{IR} channels (668, 903, 1084, 1326), the currents measured by Edwards and colleagues (372, 373) could have originated from either cell type. Specific currents through Ba^{2+}-sensitive K_{IR} channels in vascular SMCs were first demonstrated in SMCs from rat posterior cerebral arteries by Quayle et al. (1186) and subsequently identified in SMCs from rat (1207) and pig coronary arteries (1185); hamster cremaster arterioles (185); rat renal afferent arterioles (245, 840); hamster retractor feed arteries (1313); and rat renal interlobular arteries (247). The expression and function of K_{IR} channels appears to be inversely related to vessel diameter with microvascular SMCs displaying higher functional expression than upstream arteries (903, 1128, 1185, 1187).

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Expression of K_{IR} channel transcripts and robust Ba^{2+}-sensitive K_{IR} channel currents were observed in SMCs isolated from small mesenteric arteries from inbred normotensive and hypertensive mouse strains (BPN and BPH mice) (1373). In contrast, while mRNA for K_{IR} 2.1 has been reported in SMCs from rat mesenteric arteries (168, 177, 1313), patch-clamp studies of SMCs isolated from small mesenteric arteries in rats (291, 1313) and some mice strains (1326) have failed to identify Ba^{2+}-sensitive K_{IR} channel currents. Lack of functional evidence for K_{IR} channels in rat mesenteric arteries also has been presented (177). These data conflict with a report of robust expression of K_{IR} 2.1 transcripts from primary cultures of SMCs isolated from rat mesenteric arteries, with highest expression observed in third-order branches off of the superior mesenteric artery. Substantial Ba^{2+}-sensitive currents recorded from these cells and Ba^{2+}-sensitive, K^+-induced vasodilation was observed in endothelium-denuded rat mesenteric arteries (749). There is no current explanation for these conflicting results, but it may be related to differences in animal strains, species or methods.

Vascular SMCs have been reported to express only K_{IR} 2.1 (168, 1130), or K_{IR} 2.1 and 2.2 (670, 689, 1313, 1373, 1551). However, in the mouse, knockout of K_{IR} 2.1 eliminates K_{IR} channel currents in cerebral SMCs from neonates (1621). These data suggest that, at the least, K_{IR} 2.1 is essential for K_{IR} channel currents in this model. K_{IR} 2.1 also has been proposed to compose the K_{IR} channels that are observed in rat afferent arteriole SMCs (245, 840). In the myocardium where K_{IR} 2.1, 2.2 and 2.3 are expressed, it has been proposed that channels composed of predominately K_{IR} 2.1/2.2 heteromers underlie the native K_{IR} channel currents (1652). Here too, knockout of K_{IR} 2.1 abolishes native K_{IR} currents indicating a critical role for K_{IR} 2.1 in the native channels (1622).

Pharmacology of K_{IR} channels

The primary pharmacological tool for the study of K_{IR} channels in cells, tissues, and *in vivo* has been Ba^{2+} ions (Table 2). Early studies identified Ba^{2+} ions as potent and effective inhibitors of K_{IR} channels (533). Extracellular Ba^{2+} produces voltage-dependent block of strongly rectifying K_{IR} channels: at physiological membrane potentials (−30 to −40 mV), the K_d for Ba^{2+} block of whole-cell K_{IR} channels currents in rat cerebral artery SMCs is on the order of 8 to 10 μmol/L (1186), with concentrations up to 300 μmol/L required for complete block. These data are consistent with the block of K_{IR} channels in other systems. Note that Ba^{2+} also blocks K_{ATP} channels with an IC_{50} = 100 μmol/L (154), so appropriate controls must be implemented when using higher concentrations of this ion. Cesium ions also block the channel in a voltage-dependent manner (594). More recently, a small molecule inhibitor of K_{IR} 2 channels, ML133, has been reported (1496). However, there are as yet no complete studies of the action of this drug on vascular SMC K_{IR} channels, and it should be noted that ML133 also blocks K_{ATP} channels composed of K_{IR} 6.2 subunits (1496).

K_{IR} channels and myogenic tone

Currents through K_{IR} channels contribute to resting membrane potential and tone of isolated SMCs, and SMC's in isolated resistance arteries and arterioles from several vascular beds. Extracellular Ba^{2+} was reported to depolarize unpressurized male guinea pig submucosal arterioles (372) and male rat cerebral arterioles (373) suggesting that K_{IR} channels

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contribute to the resting membrane potential of SMCs in these vessels. Consistent with this hypothesis, Ba^{2+} has also been shown to constrict male rat posterior cerebral arteries (973), constrict cerebral and brainstem penetrating arterioles (619), depolarize and constrict hamster cremaster arterioles (185), constrict male hamster retractor feed arteries (689), constrict male (711) and female (1313, 1551) rat middle cerebral and coronary septal arteries (1313), depolarize (245, 246), and constrict (245, 246, 1429) male rat renal afferent arterioles and interlobular arteries (247) in pressure myography studies, *in vitro*. Micromolar concentrations of Ba^{2+} also have been reported to depolarize guinea pig spiral modiolar artery SMCs (703).

In contrast, in female rat posterior cerebral arteries and coronary septal arteries, Ba^{2+} was reported to have little effect on resting membrane potential or diameter (766). No effect of Ba^{2+} on resting tone of isolated porcine coronary arterioles also has been reported (1204). Similarly, Ba^{2+} had no effect on resting tone of rat parenchymal arterioles in brain slices (426). These data suggest that experimental conditions may modulate the function of K_{IR} channels.

Consistent with the *in vitro* studies of isolated SMCs and cannulated, pressurized vessels presented above, there also are *in vivo* data supporting a role for K_{IR} channels in the control of resting vascular tone and blood flow. It should be noted, however, that the *in vivo* experiments are difficult to interpret because the site of action of Ba^{2+} (SMCs, endothelial cells, parenchymal cells, nerves, etc.) cannot be established, and because of often complex compensatory mechanisms. Nonetheless, micromolar concentrations of Ba^{2+} constrict cremaster arterioles in both anesthetized rats (898) and hamsters (63, 1596). Rat (970, 1359) and cat (371) pial arterioles also constrict in response to Ba^{2+}. With the exception of one study (292), infusion of Ba^{2+} into human forearm [plasma concentrations of Ba^{2+} of ~50 μmol/L (318)] causes vasoconstriction (294, 295, 318). Given that the arteriolar endothelium poses a significant barrier to the passage of charged molecules (848), the precise concentration of Ba^{2+} to which the vascular SMCs were exposed in these *in vivo* experiments is unknown. In contrast, topically applied Ba^{2+} reportedly has no effect on resting cerebral blood flow in anesthetized mice (479). Thus, the bulk of evidence indicates that K_{IR} channels are active in resistance arteries and arterioles at rest and contribute to resting membrane potential, tone and tissue blood flow.

K^+-induced vasodilation: Functional evidence for vascular K_{IR} channels

Extracellular K^+ has long been proposed as an important signaling molecule that may be involved in the mechanisms responsible for matching tissue blood flow with the level of activity in electrically excitable tissues (531). In addition, K^+ released from adjacent endothelial cells may accumulate in the intercellular space next to SMCs and also provide a signal coupling endothelial cell K^+ channel activation to SMC function (186, 531). Thus, a large number of studies have examined the effects of elevated extracellular K^+ on vascular tone and blood flow either as tests of the hypothesis that K^+ is a mediator of functional vasodilation or, as will be seen, as a sensitive assay for the presence and function of vascular K_{IR} channels (Fig. 7).

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Early studies showed that isotonic elevation of extracellular K^+ causes vasodilation and a decrease in vascular resistance in canine forelimb (441, 1119), coronary (1273), renal (441), gastrointestinal (1401), and cerebral (805) circulations. However, the site of action of the elevated K^+ concentration (SMCs, endothelial cells, and parenchymal cells) and its precise mechanism of action could not be established. Subsequently, Edwards et al. (373) showed that small cerebral arterioles hyperpolarized when exposed to small elevations in extracellular K^+ concentration and that this effect could be blocked by micromolar concentrations of Ba^{2+}, suggesting that K_{IR} channels were part of the mechanism of action. However, as these experiments were performed on intact arterioles, the site of action of the K^+ and Ba^{2+} could not be established. Later, in isolated cerebral (711, 766, 972, 973) and coronary (766) resistance arteries it was shown that these vessels dilate when exposed to elevated extracellular K^+ from a resting level of 3 to 5 mmol/L up to approximately 20 mmol/L, that these dilations were preceded by SMC hyperpolarization (766) and that these K^+-induced effects could be blocked by micromolar concentrations of Ba^{2+}. Furthermore, removal of the endothelium did not eliminate the responses to elevated K^+, targeting the effects to the SMCs. Barium also blocks K^+-induced dilation of rat afferent arterioles (245, 246), rat interlobular arterioles (247), and parenchymal arterioles studied by pressure myography and in brain slices (426, 902) supporting a role for K_{IR} channels in a variety of vascular SMCs.

It should be noted that not all K^+-induced vasodilation can be explained by SMC K_{IR} channels. For example, in rat cerebral arteries, dilation of isolated vessels induced by exposure to 5 mmol/L K^+ after exposure to 0 mmol/L K^+ is mediated by the Na^+/K^+ ATPase and can be inhibited by ouabain (973). In these vessels elevation of K^+ from 5 mmol/L to higher levels up to 20 mmol/L results in dilation that is fully blocked by Ba^{2+}. These data suggest that there are two independent mechanisms of action dependent on the K^+ range and the initial conditions. In human forearm, vasodilation induced by infusion of KCl is attenuated by infusion of Ba^{2+} (~50 μmol/L in plasma) (318), but is abolished by ouabain + Ba^{2+} (292, 318). In isolated hamster cremaster arterioles (185), K^+-induced SMC hyperpolarization and dilation are only attenuated by Ba^{2+} at a concentration that was shown to fully block vascular K_{IR} channels, whereas the Na^+/K^+ ATPase inhibitor, ouabain, alone, abolished K^+-induced vasodilation. Burns et al. (185) proposed that the K_{IR} channels in this system acted mostly to amplify hyperpolarization produced by K^+-induced activation of the Na^+/K^+ ATPase in these hamster arterioles. It should be noted, that in mouse cremaster arterioles, Ba^{2+} alone abolishes K^+-induced dilation, suggesting that only K_{IR} channels mediate K^+-induced dilation in these arterioles (Jackson, unpublished observations). In rat renal arcuate arteries, K^+-induced dilation appears to be mediated solely by the Na^+/K^+ ATPase, with no role for K_{IR} channels (1175). These data suggest that there may be regional and/or species differences in the function of K_{IR} channels in resistance arteries and arterioles.

Vasoconstrictors and K_{IR} channels

K_{IR} channels are open under resting conditions in SMCs of resistance arteries and arterioles (see above). Thus, closure of these channels by signaling pathways activated by vasoconstrictors could contribute to the membrane depolarization that is observed when

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these vessels constrict. Studies in the literature have shown that signaling pathways that are commonly activated by vasoconstrictors such as those involving PKC (591, 1653) or tyrosine kinases (1540, 1652) can inhibit K_{IR} 2-containing K_{IR} channels (Fig. 7).

Currents through K_{IR} channels in rabbit coronary SMCs are inhibited by α_1-adrenergic receptor activation, although the signaling pathway that was involved was not investigated (1567). Both endothelin-1 (1130) and angiotensin II (1133) inhibit currents through K_{IR} channels in rabbit coronary SMCs through PKC α-dependent mechanisms that were mimicked by phorbol 12,13-dibutyrate or 1-oleoyl-2-acetylsn-glycerol, direct activators of PKC (1130). Endothelin also has been shown to inhibit K_{IR} channel currents in endothelial cells (1629). In addition, superfusion with phorbol 12,13-dibutyrate inhibits K^+-induced dilation of rat pial arterioles, *in vivo* (1476). These data suggest that vasoconstrictors that act on $G_{q/11}$-coupled receptors to activate the PLCβ-DAG-PKC signaling cascade have the potential to inhibit vascular SMC K_{IR} channels, which would contribute to vasoconstrictor-induced SMC depolarization (Fig. 7). However, it has also been shown that phorbol ester-induced activation of PKC inhibits K^+-induced dilation of rat cerebral arteries without affecting K^+-induced hyperpolarization, data that argue against PKC-dependent inhibition of K_{IR} channel function (249). These data also indicate that inhibition of K^+-induced dilation does not always mean a reduction of K_{IR} channel function.

Vasoconstrictor-induced inhibition of K_{IR} channel function may be vessel and agonist specific. For example, UTP, the thromboxane analog, U46619 and 5-HT had no effect on K_{IR} currents in SMCs from female rat cerebral arteries (1551). All 3 of these agonists act on receptors coupled to the $G_{q/11}$ signaling cascade, as do endothelin-1 and angiotensin II, noted above (1133). In these same cerebral SMCs it was shown that direct activation of PKC using phorbol esters, or hypoosmotic challenge rapidly inhibited K_{IR} channel currents in a PKC-dependent manner (1551). These data suggest that there may be regional or species-dependent differences in the signaling pathways coupled to K_{IR} channels. The studies by Wu et al. (1551) also suggest that, in the cerebral circulation, inhibition of K_{IR} channels may contribute to pressure- or stretch-induced depolarization of these cells. However, these findings are difficult to reconcile with previous studies showing lack of effect of PKC activation on K^+-induced SMC hyperpolarization (249).

The specific K_{IR} channel isoform involved in vasoconstrictor-induced inhibition of vascular K_{IR} channels has not been established. Studies in heterologous expression systems have shown that activation of PKC via phorbol 12,13-dibutyrate or phorbol mysterate acetate inhibits currents through K_{IR} 2.3 channels [and by inference, K_{IR} 2.2 channels (344, 1653), but not K_{IR} 2.1 channels (344, 591)]. These data suggest that PKC-dependent effects may involve K_{IR} 2.2 alone or heteromeric channels containing K_{IR} 2.2.

However, activation of α_{1A}-adrenergic receptors, which also is coupled to $G_{q/11}$, inhibits currents through homomeric K_{IR} 2.2 channels and heteromeric K2.1/2.2 channels, but not K_{IR} 2.1 channels in a heterologous expression system by a mechanism involving Src tyrosine kinases, independent from PKC (1652), which also has inhibitory effects on K_{IR} 2.2-containing channels (1653). A Src tyrosine kinase was also shown to mediate α_{1A}-adrenergic receptor mediated inhibition of native K_{IR} channel currents in rat ventricular

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myocytes which are likely heteromers of K_{IR} 2.1 and 2.2 (1652). In contrast, α_{1A}-adrenergic receptor-mediated modulation of K_{IR} 2.3 channels is mediated by PKC (1652). Also, K_{IR} 2.3 is inhibited by $G\beta\gamma$-subunits when expressed as homomers or heteromers with K_{IR} 2.1 (267). Thus, the specific K_{IR} channel isoforms and the signaling pathways involved in vasoconstrictor-induced inhibition of K_{IR} channel currents in vascular SMCs remain in question.

Vasodilators and K_{IR} channels

Increased activity of K_{IR} channels will produce membrane hyperpolarization and vasodilation, and, as will be outlined below, studies support a role for K_{IR} channels in the mechanism of action of several vasodilators. However, it should also be noted that currents through K_{IR} channels can be recruited simply by membrane hyperpolarization due to activation of other K^+ channels, for example, with K_{IR} channels acting to amplify the initial hyperpolarization (668, 689, 903, 1313, 1326) (Fig. 7). SMC K_{IR} channels also have the potential to be activated by K^+ ions released during activation of endothelial cell K^+ channels (i.e., endothelial-derived hyperpolarization at myoendothelial junctions) (186, 531, 903).

Barium inhibits bradykinin-induced dilation of coronary arterioles implicating K_{IR} channels in the mechanism of action of this dilator (1204). These channels also participate in propagation of hyperpolarizing signals along arterioles (689, 1204, 1313). Inward rectifier K^+ channels also have been proposed to contribute to bradykinin-induced dilation in human forearm (356). C-type natriuretic peptide, a putative endothelium-derived hyperpolarizing factor (EDHF) may act, in part, by activation of K_{IR} channels (222).

cAMP signaling and K_{IR} channels—In other systems, K_{IR} channels can be modulated by protein kinases (1540) or G-proteins (726) suggesting that their vascular counterparts may also be regulated in a similar fashion. Adenosine activates currents through Ba^{2+}-sensitive K_{IR} channels in rabbit small coronary artery SMCs and increases coronary blood flow via a mechanism involving A_3-adenosine receptors, adenylate cyclase, cAMP and PKA (1323). Adenosine-induced dilation of pial arterioles is inhibited by Ba^{2+}, inhibitors of adenylate cyclase and PKA (1125) also supporting a role for cAMP-PKA signaling pathway in modulating the function of vascular K_{IR} channels. Hypoxia activates K_{IR} channels in rabbit small coronary artery SMCs through a mechanism involving G_s, adenylate cyclase, cAMP and PKA (1129). Thus, there is support for cAMP-PKA mediated activation of vascular K_{IR} channels (Fig. 7).

NO-cGMP-PKG signaling and K_{IR} channels—Additional studies in porcine pial arterioles demonstrated a second, potentially species-specific signaling pathway in which adenosine acts on endothelial cells to stimulate NO production that then relaxes pial SMCs via a Ba^{2+}-sensitive mechanism (582). These data suggest that NO may activate SMC K_{IR} channels in this preparation, although the precise signaling pathway was not established (582). SNP activates K_{IR} channels composed of K_{IR} 2.1 channels in rat tail artery SMCs and contributes to vasodilation induced by this NO donor in that tissue (1269) (Fig. 7). In

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addition, Ba^{2+} inhibits relaxation of rat tail artery to the PGI_2 receptor agonist, cisaprost, through a mechanism that does not appear to be mediated by PKA (1112).

Heterologous expression systems have provided further insight into the regulation of K_{IR} channels. Currents through K_{IR} 2.2 channels are increased by activated PKA through phosphorylation of S430 (1653). Additional studies have shown that activation of β_3-adrenoreceptors increases currents through K_{IR} 2.1 and K_{IR} 2.2 channels (1259). For K_{IR} 2.1, this appears to involve PKC, for K_{IR} 2.2, cAMP and PKA-mediated activation (1259). Heteromeric channels containing K_{IR} 2.1 and 2.2 were regulated similar to homomeric K_{IR} 2.2 channels (1259).

Functional vasodilation and K_{IR} channels

There is considerable evidence that K_{IR} channels contribute to functional vasodilation in skeletal muscle and in the brain. In hamster cremaster muscles, Ba^{2+} attenuates vasodilation induced by muscle contraction, particularly the rapid onset of dilation, suggesting a role for K_{IR} channels in coupling muscle contraction to vascular function in this tissue (63). Studies in human forearm also have shown that Ba^{2+} inhibits the rapid-onset vasodilation induced by muscle contraction (293), as well as the steady-state functional vasodilation in that tissue (294). Barium also attenuates reactive hyperemia induced by blood flow occlusion to the forearm, supporting a role for K_{IR} channels in this response (295).

Barium ions reduce hypoxia-induced coronary vasodilation in Langendorff-perfused rabbit hearts that involves adenylate cyclase, cAMP and PKA suggesting a role for the K_{IR} channels in hypoxia-induced vasodilation in this preparation (1129, 1136).

Arteriolar K_{IR} channels also play a role in neurovascular coupling in the brain. Barium attenuates electrical field-stimulation-induced dilation of parenchymal arterioles in brain slices (426). Barium also has been shown to reduce functional vasodilation induced by whisker stimulation in the mouse cerebral cortex (479), and vasodilation of pial arterioles induced by peripheral nerve stimulation (1125, 1476).

K_{IR} channels and pathophysiology

Hypertension—Early studies demonstrated that K^+-induced vasodilation in dog hindlimb (1116), rat hindlimb (1117) and human forearm (1118) was impaired with hypertension. These data are consistent with a reduced function of K_{IR} channels in hypertension.

However, several subsequent studies in isolated vascular preparations found that K^+-induced relaxation of strips of rat tail artery (1504), pig tail artery (1503) or rat basilar artery (592) was increased in vessels from hypertensive animals. However, in all of these *in vitro* studies, vessels were exposed to solutions with 0 mmol/L K^+ to induce K^+ reactivity. It was later shown that in isolated cerebral vessels, the SMC response to elevated K^+ after exposure to 0 mmol/L K^+ was largely mediated by the Na^+/K^+ ATPase, whereas K^+-induced dilation initiated from physiological K^+ levels (3–5 mmol/L K^+) were Ba^{2+}-sensitive and likely mediated by K_{IR} channels. Further, the K_{IR} channel-mediated responses were reduced in vessels from hypertensive rats (972).

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Dilation of basilar arteries to increased K^+ was elevated in SHR (250). However, these K^+-induced dilations in the SHR were relatively insensitive to block by Ba^{2+}, in contrast to what is observed in basilar arteries in normotensive WKY rats (250). Instead, the augmented response in the SHR resulted from nNOS-derived NO released from perivascular nerves (250). These data suggest that there is a loss of K_{IR} channel function in hypertension with compensatory upregulation of the nNOS pathway to maintain reactivity to elevated K^+.

Expression of K_{IR} 2.1 was reduced in mesenteric SMCs from hypertensive BPH mice relative to normotensive controls (BPN) (1373). The decreased expression correlated with a decrease in K_{IR} channel current density in SMCs, SMC depolarization, and increased myogenic reactivity of resistance arteries from BPH that may contribute to the hypertensive phenotype in this model of essential hypertension (1373). However, despite the reduction in K_{IR} currents, Ba^{2+}-induced constriction of mesenteric arteries was not reduced in vessels from the hypertensive BPH mice (1373). These data suggest that despite reduced expression and currents, that the function of K_{IR} channels was maintained, likely by remodeling of other ion channels in the SMCs of the BPH mice to maintain homeostasis (1373).

In rats, angiotensin II-induced hypertension reduces SMC K_{IR} channel current density and K^+-induced dilation of skeletal muscle and cerebral arteries (1281). In the skeletal muscle artery SMCs, 2 weeks of exercise training reversed the effects of hypertension on K_{IR} channel currents and K^+-induced dilation (1281). While K_{IR} channel currents were restored by exercise in cerebrovascular myocytes, K^+-induced dilation remained depressed (1281) suggesting regional heterogeneity in the response to exercise training. Previous studies showed that exercise training augments expression and function of vascular SMC K_{IR} channels (709).

In contrast to the findings outlined earlier, Ba^{2+}-sensitive, K^+-induced dilation of parenchymal arterioles in rat cerebral cortex was augmented in brain slices from SHR compared to arterioles in brain slices from normotensive WKY (1047). This may indicate that there are regional differences in the impact of hypertension on K_{IR} channel expression and function in the vasculature.

Obesity and the metabolic syndrome—The effects of obesity and the metabolic syndrome on vascular SMC K_{IR} channels have not been well studied. Diet-induced obesity is associated with reduced K_{IR} channel function in rat mesenteric arteries (528), although this likely represents effects on endothelial cell K_{IR} channels and not channels in SMCs. K^+-induced vasodilation in human forearm is reduced in obese subjects (1479), suggesting reduced K_{IR} channel function. Consistent with this hypothesis, Ba^{2+}-induced vasoconstriction was also depressed in the forearms of obese subjects (1479) and in subjects infused with elevated levels of non-esterified fatty acids (320). These data suggest that K_{IR} channel function may be decreased in the obese, which could significantly impact peripheral vascular function. Additional research will be required to precisely define the effects of obesity on K_{IR} channel function in the SMCs of resistance arteries and arterioles around the body.

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Diabetes—The effects of type 1 diabetes on K_{IR} channel function is not clear, because there is evidence for both increased and decreased function in animal models of this disease. Ba^{2+}-induced constriction of afferent arterioles is increased in streptozotocin-induced diabetic rats (1429, 1430), with no change in expression of mRNA or protein for K_{IR} 2.1 (1430). The increased Ba^{2+}-induced constriction could be normalized by treatment with the superoxide dismutase mimetic, Tempol, suggesting a role for ROS in mediating the increased K_{IR} channel function (1430). No change in mRNA expression of K_{IR} 2.1 in aortic SMCs from streptozotocin-induced diabetic rats has also been reported (1197). These data suggest that K_{IR} channel function is upregulated in diabetes, with no change in expression.

In contrast to the studies of renal arterioles cited above, studies of pial arterioles suggest that K_{IR} channel function is impaired in diabetes. Barium-induced constriction and K^+-induced dilation were impaired in pial arterioles of streptozotocin-induced diabetic rats (970), suggesting reduced K_{IR} channel function. Similarly, K_{IR} channel function in pial vessels was impaired in diabetes through a mechanism involving PKC (1476). Diabetes was associated with an increase in the rectification of K_{IR} currents in pericytes located at the arteriolar end of capillaries in the retinas of streptozotocin-treated rats (962). This results in a decrease in the outward “hump” in the current positive to the K^+ equilibrium potential, and a slight depolarization of these cells (962). The increased rectification appears to be caused by increased spermine production in this model of diabetes. Thus, there may be regional differences in the effects of diabetes on K_{IR} channel function.

Hypercholesterolemia—As noted above, K_{IR} 2.1 and 2.2 are strongly regulated by membrane cholesterol, and hypercholesterolemia results in silencing of endothelial cell K_{IR} channels (400). However, comparable studies have yet to be performed on SMC K_{IR} channels. In a rat model, K_{IR} 2.1 mRNA expression was unchanged by hypercholesterolemia, but K_{IR} channel function was not examined (1198). In humans, infusion with elevated levels of non-esterified fatty acids reduces the magnitude of Ba^{2+}-induced vasoconstriction, suggesting reduced K_{IR} channel function (320). In mouse models of hypercholesterolemia, conducted vasodilation, which may involve SMC K_{IR} channels (689, 1313), is not impaired (109, 1542). Although not directly tested, these data suggest no impairment of K_{IR} channel function in this model of hypercholesterolemia. Reactive hyperemia of second-order arterioles is impaired in hypercholesterolemic mice (1466), although a specific role for K_{IR} channels was not assessed. Thus, the effects of hypercholesterolemia on SMC K_{IR} channel expression and function remain unclear.

Other disease states—Subarachnoid hemorrhage converts K^+-induced dilation into K^+-induced constriction due to elevated release of K^+ from glial BK_{Ca} channels, with no change in the function of parenchymal arteriolar K_{IR} channels (775). Stress impairs K_{IR} channel function in rat cerebral parenchymal arterioles, which, in turn, reduces neurovascular coupling potentially contributing to the reduced cognitive function associated with stress (902). There is increased angiotensin II-induced inhibition of K_{IR} channels in small coronary arteries after isoproterenol-induced cardiac hypertrophy (1134). Potassium ion-induced vasodilation is impaired after ischemia/reperfusion injury in middle cerebral arteries (944), although the mechanism was not explored. Similarly, brain ischemia reduces K_{IR}

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currents in cerebrovascular SMCs in the rat (94, 95). Pretreatment with LPS eliminates the decrease in functional K_{IR} channels and K^+-induced vasodilation after ischemia (95).

K_{ATP} Channels

Discovery of K_{ATP} channels

Noma discovered ATP-sensitive K^+ channels in cardiac myocytes (1097), and currents through similar channels were subsequently identified in many other cell types including vascular SMCs [see (9, 15, 68–72, 76, 166, 180, 219, 272, 273, 311, 322, 374, 375, 436, 506, 544, 661, 786, 826, 827, 984, 1070, 1111, 1182, 1183, 1187, 1188, 1332, 1464, 1595, 1604) for reviews]. These K^+ channels derive their name from their property that increases in intracellular ATP decrease their activity. However, and probably of more physiological relevance, their activity is modulated by a number of signaling pathways independent from their ATP sensitivity.

Structure and Expression of K_{ATP} channels

K_{ATP} channels are hetero-octamers composed of four inward rectifier K^+ channel subunits in the K_{IR} 6.X family, coupled with four regulatory subunits, the so-called sulfonylurea receptors (SURs) (15, 76, 1187). The hallmark ATP sensitivity of these channels resides in the K_{IR} 6.X channel subunits as indicated by site directed mutagenesis of K_{IR} 6.2 (1436, 1437), which is the pore-forming subunit in cardiac myocytes (1363). Vascular SMCs express K_{IR} 6.1 subunits (75, 855, 1001, 1013, 1363), as suggested by Yamada et al. (1570). However, K_{ATP} channels that are heteromultimers of K_{IR} 6.1 and 6.2 have been described in guinea pig urethral SMCs (1398), suggesting that there could be regional variability in the structure of SMC K_{ATP} channels.

The regulatory SUR subunits confer sensitivity to blockade by sulphonylureas, such as tolbutamide and glibenclamide, and also are necessary for activation of the channels by K_{ATP} channel openers such as diaxozide, cromakalim and pinacidil, as well as nucleotide diphosphates (15, 76, 1187). There are two different classes of SUR subunits, with expression varying by cell type. The type of SUR expressed determines the sensitivity to blockade of the channels by sulphonylureas, and possibly the sensitivity to activation by K_{ATP} channel openers (15, 76, 1187). Pancreatic β-cells express a 140 kDa receptor that has been termed SUR1, which has a high affinity for glibenclamide (K_d ~ 10 nM) (15, 76, 1187). Cardiac myocytes and vascular SMCs express sulphonylurea receptors that are in the SUR2 class. These receptors show 68% homology to SUR1, and have an affinity for glibenclamide that is more than an order of magnitude lower (100–600 nmol/L) than SUR1 (15, 76, 1187). There are two spliced variants of SUR2 (SUR2A and SUR2B) (644, 660, 1570); vascular muscle cells express the SUR2B isoform of these receptors (10, 1013, 1187).

Pharmacology of K_{ATP} channels

Sulfonylureas, such as glibenclamide (Table 2), block K_{ATP} channels by binding to their SUR subunits, and are the primary tools used to study K_{ATP} channels *in vitro* and *in vivo*. At concentrations of 1 μmol/L or less, glibenclamide is very selective. However, because this

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drug has to diffuse through the plasma membrane to bind to the intracellular SUR, it has a slow rate of onset of effect [>15 min in organ bath type experiments to achieve maximal blockade (990)]. Therefore, particularly in patch clamp experiments, many investigators have resorted to using higher concentrations, such that the time to maximal block is reduced. However, in whole tissue experiments, and *in vivo*, the use of concentrations higher than 1 μmol/L is fraught with difficulties because glibenclamide can have significant off-target effects including nonspecific vasodilation (705) and block of Cl^- channels (1627). Caution is also urged with the use of the K_{ATP} channel agonist, pinacidil, because at concentrations higher than 10 μmol/L, this drug relaxes vascular SMCs by mechanisms other than activation of K^+ channels (991).

K_{ATP} channels and myogenic tone

K_{ATP} channels contribute to resting vascular tone and tissue blood flow in the coronary (128, 305, 354, 407–409, 641, 674, 995, 996, 1029, 1193, 1202, 1203, 1246, 1286, 1336, 1644), skin (2, 196, 613), splanchnic, and renal circulations (351, 614). In the heart it has been shown that the beating myocardium releases a K_{ATP} channel agonist that activates these channels and dilates coronary arterioles (1376).

In the resistance vasculature of skeletal muscle there is evidence both for (664, 784, 1231, 1462, 1463) and against (85, 86, 137, 351, 405, 406, 547, 614, 1041) a contribution of K_{ATP} channels to resting vascular tone and blood flow. The reason for these different findings has not been established, but could relate to methodological differences. For example, it has been shown that the rate of inhibition of K_{ATP} channels by glibenclamide is quite slow, requiring up to 15 min for maximal block to occur (990). In addition, glibenclamide has been shown to nonspecifically relax SMCs with an EC_{50} = 40 μmol/L (705) (the IC_{50} for block of K_{ATP} channels is on the order of 100 nmol/L for vascular K_{ATP} channels). Thus, constriction due to block of K_{ATP} channels by glibenclamide may have been offset by nonspecific vasodilation dependent on the concentration of glibenclamide used and the duration of exposure to the K_{ATP} channel blocker. In addition, particularly in human studies with infused glibenclamide, there is substantial binding of this drug to plasma proteins such that the free concentration of the drug available to block SMC K_{ATP} channels will be low. Also, lower concentrations of the blockers are usually used in human studies (137).

K_{ATP} channels do not appear to be active in the cerebral circulation under resting conditions in a variety of model systems [see (402) for numerous references and (618, 838, 877, 1096, 1422, 1510)].

Vasoconstrictors and K_{ATP} channels

Vasoconstrictors decrease K_{ATP} channel activity through several mechanisms. Considerable evidence indicates that PKC inhibits K_{ATP} channels (155, 249, 268, 570, 1190, 1249) both by altered channel gating (268) and by promoting internalization of the channels (708) (Fig. 8). Vasoconstrictor agonist-induced elevation of intracellular Ca^{2+}, acting through PP2B (calcineurin), also has been shown to inhibit K_{ATP} channel function (1537) (Fig. 8). Finally, vasoconstrictors that signal through $G_{i/o}$ can inhibit constitutively active adenylate cyclase to reduce K_{ATP} channel activity (570). Vasoconstrictors that have been shown to inhibit K_{ATP}

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channels include angiotensin II (570, 1016), endothelin (1018), histamine (155, 762), norepinephrine (666), neuropeptide Y (155), phenylephrine (155), 5-HT (155, 762), and vasopressin (1291, 1487) (Fig. 8). Closure of K_{ATP} channels also has been implicated in vasoconstriction of cremaster arterioles induced by the α_2-adrenergic agonist, UK-14,304 (1393), although the mechanism responsible for this effect was not established. Inhibition of K_{ATP} channels by angiotensin II has been shown to involve PKCε (570, 1249) and its recruitment to caveolae (1249). This isoform of PKC also is responsible for signaling internalization of K_{ATP} channels from caveolae (708). Studies of K_{IR} 6.2-containing-K_{ATP} channels have shown that the channels undergo constitutive, rapid endocytosis and recycling, and that PKC reduces recycling and targets the channels for lysosomal destruction (940). It is assumed that a similar process is involved in PKC-dependent internalization of K_{ATP} channels in the vascular K_{IR} 6.1-containing channels.

Vasodilators and K_{ATP} channels

cAMP-PKA signaling and K_{ATP} channels—K_{ATP} channels have been implicated in the mechanism of action of vasodilators that are thought to act through the cAMP-signaling cascade such as adenosine (24, 308, 664, 761, 1193), PGI_2 (161, 664), PGE_1 (378), PGE_2 (161), CGRP (759, 1072, 1184, 1520), vasoactive intestinal peptide (1257, 1592), and agonists of β-adrenergic receptors (664, 1005, 1048, 1068) (Fig. 8). This involves receptor-mediated activation of adenylate cyclase type 6 [AC6 (1068)], formation of cAMP and activation of PKA, which is targeted to the channels by AKAPs (569), with the channels localized in caveolae (1250). Exogenous caveolin-1 inhibits K_{ATP} channel activity suggesting that localization in caveolae is also important in regulation of the channel's basal activity (313). Phosphorylation of both the K_{IR} 6.1 (1191) and SUR2B (1290, 1296) subunits by PKA underlies the effects of cAMP-related vasodilators on K_{ATP} channel activity in vascular SMCs.

NO-cGMP-PKG signaling and K_{ATP} channels—There is evidence both for and against NO and cGMP signaling in modulating the activity of K_{ATP} channels in vascular SMCs (Fig. 8). Patch clamp studies of vascular SMCs from porcine coronary arteries found that NO, via activation of guanylate cyclase, increases the activity of K_{ATP} channels (1017). Similarly, atrial natriuretic peptide, an NO-donor and 8-Br-cGMP activated K_{ATP} channels in cultured rat aortic vascular SMCs (793). Nitric oxide was also shown to hyperpolarize SMCs in rabbit mesenteric arteries via a mechanism that involves cGMP and activation of K_{ATP} channels (1040). Hyperpolarization induced by NO was also shown to involve K_{ATP} channels in mesenteric SMCs (1547). K_{ATP} channels have also been implicated in vasodilation induced by NO in several other systems (57, 581).

However, studies in rabbit coronary circulation (674), rabbit mesenteric arteries (743, 1184), porcine retinal arterioles (478) and mouse mesenteric arteries (1043) have failed to demonstrate a role for K_{ATP} channels in the mechanism of action of exogenous NO, NO-donors or endothelium-derived NO. The reasons for this heterogeneity are not clear, but may indicate that subtle differences in methodology affect coupling of the NO-cGMP-PKG signaling pathway to K_{ATP} channels, and that there are regional or species differences in mechanisms that modulate these channels.

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The mechanism by which NO activates K_{ATP} channels in vascular SMCs has not been firmly established. In cardiac myocytes, NO-induced activation of K_{IR} 6.2-based K_{ATP} channels involves cGMP, PKG, ERK1/2, and CAMK II (1625). It has also been speculated that NO-induced cGMP formation may cross-activate PKA to modulate K_{ATP} channel activity (1187).

Other dilators and K_{ATP} channels—Hydrogen sulfide also appears to act, at least in part, by activation of K_{ATP} channels. This gasotransmitter was shown to activate K_{ATP} channel currents in rat aortic SMCs, and H_2S-induced relaxation of rat aortas could be inhibited by very high concentrations of glibenclamide (1636). Glibenclamide also was shown to inhibit H_2S-induced vasodilation of perfused rat mesenteries (238) and canine myocardium (202), consistent with a role for K_{ATP} channels in its mechanism of action. H_2S also has been shown to activate K_{ATP} channels in cerebral arteriolar SMCs to cause vasodilation (838, 869). H_2S appears to sulfhydrate K_{ATP} channels leading to their activation and subsequent vasodilation (1043).

Acidosis-induced dilation of coronary arterioles is mediated by K_{ATP} channels (659). Hypercapnic acidosis-induced increases in blood flow are inhibited by glibenclamide in mouse hearts (583) and in the cerebral circulation (401, 877).

Early studies showed that hypoxic dilation of the coronary circulation could be reduced by glibenclamide (310, 1049, 1050, 1483). Similar results have been obtained in the cerebral (1370, 1416), systemic (945), and renal (906) circulations. Although hypoxia has been demonstrated to activate K_{ATP} channels in SMCs from rabbit coronary arteries (309), other studies have suggested that hypoxia stimulates endothelial cells to release PGI_2 (437) [or other substances (882)], or parenchymal cells to release adenosine (883, 945, 1050, 1483) or opioids (56) which then activate SMC K_{ATP} channels to hyperpolarize SMCs and produce vasodilation. However, in fetal pigs, hypoxia-induced pial arteriolar vasodilation does not involve K_{ATP} channels (839) and in rat coronary resistance arteries endothelium-derived NO appears to mediate hypoxic vasodilation (915). Hypoxia-induced cerebral vasodilation in the rat also involves EETs (883).

Volatile anesthetics such as halothane (819), isoflurane (203, 296, 447), and enflurane (296) cause coronary vasodilation that can be inhibited by glibenclamide. Similar results have been reported for volatile anesthetic-induced dilation of pial arterioles (637). In isolated porcine coronary arterioles, isoflurane-induced dilation is endothelium dependent and can be inhibited by glibenclamide (457). However, isoflurane has been shown to activate K_{ATP} channel currents in isolated vascular SMCs and that activation of K_{ATP} channels by isoflurane requires SUR2B (447) and likely results from PKA-mediated phosphorylation of both K_{IR} 6.1 and SUR2B subunits (1381).

Functional hyperemia and K_{ATP} channels

There is evidence both for and against a role for K_{ATP} channels in the local regulation of blood flow to tissues and organs. Muscle contraction-induced dilation of arterioles in hamster cremaster muscles is inhibited by glibenclamide (547, 1041, 1231). Glibenclamide also inhibited functional hyperemia in rat (952) and mouse (1559) spinotrapezeus muscles.

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Consistent with these data, normal functional hyperemia in rat hindlimb muscles requires functional K_{ATP} channels (614). In contrast, studies in human forearm have failed to identify a role for K_{ATP} channels in exercise-induced increases in blood flow (405, 406, 1268). These data suggest that there may be species differences in the role played by K_{ATP} channels in the regulation of skeletal muscle blood flow. Methodological differences also cannot be excluded as the dose or concentration of glibenclamide used in human studies is often much lower than what is usually used in animal studies.

There is evidence both for and against a role for K_{ATP} channels contributing to functional hyperemia in the coronary circulation. Exercise-induced hyperemia in the canine coronary circulation was reduced by glibenclamide supporting a role for K_{ATP} channels in this system (353, 654). K_{ATP} channels also have been implicated in pacing-induced hyperemia in dog (736), human (408), and mouse (1644) coronary circulations. The increased coronary blood flow induced by β_1-adrenergic agonists in canine hearts also is inhibited by glibenclamide (1057). K_{ATP} channels also appear to contribute to exercise-induced vasodilation in the porcine coronary circulation (995).

In contrast, a number of studies suggest that K_{ATP} channels do not contribute to functional hyperemia in the coronary circulation. Glibencamide reduced coronary blood flow at rest, but had no effect on the increase in coronary flow produced by phenylephrine-induced hypertension and rapid atrial pacing in dogs (74). Block of K_{ATP} channels had no effect on dobutamine-induced increases in coronary flow in anesthetized female rats (1412). Glibenclamide also had little effect on increases in coronary blood flow produced by infusion of dobutamine and rapid atrial pacing in the dog (379). Similarly, pacing-induced increases in coronary blood flow were not inhibited by glibenclamide in anesthetized dogs, although this K_{ATP} antagonist did reduce resting blood flow (1202). Block of K_{ATP} channels did not alter exercise-induced vasodilation in conscious dogs (1203, 1439). Thus, there is evidence both for and against a major role for K_{ATP} channels in coupling metabolism and blood flow in the coronary circulation, with no clear explanation for the disparate findings other than the usual suspects of species and methodological differences.

Reactive hyperemia and K_{ATP} channels

K_{ATP} channels may be involved in the vasodilation and increase in blood flow that is observed after occlusion of blood flow (reactive hyperemia) in skeletal muscle. Ingestion of glybenclamide (7.5 mg) reduced resting human calf muscle blood flow and reduced both the peak and duration of the blood flow increase induced by 10 min occlusion of blood flow (784). In human forearm, block of K_{ATP} channels with tolbutamide (0.4 μmol/min) had no effect on resting blood flow or the peak increase in flow observed after 5 min occlusion (85). However, the total blood flow response (area under the curve) was reduced by K_{ATP} channel blockade (85) supporting a role for these channels in forearm reactive hyperemia. Similarly, infusion of glibenclamide to yield a plasma concentration of 60 ng/ml reduced peak flow after 2 min and flow repayment after both 2 and 5 min occlusion in human forearm (137). In contrast, infusion of glibenclamide at 0.03 μmol/min had no effect on forearm reactive hyperemia in another study (406). However, in this latter study, the infused glibenclamide

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barely inhibited dilation induced by the K_{ATP} channel agonist, diazoxide. Thus, a lack of efficacy may explain the lack of inhibition that was observed.

In the heart, K_{ATP} channels also are involved in reactive hyperemia. Daut et al. (310) first showed that glibenclamide inhibited reactive hyperemia in Langendorff-perfused guinea pig hearts, *in vitro*. Glibenclamide also inhibited reactive hyperemia induced by 15 to 120 s occlusion in canine coronary circulation, *in vivo* (73, 128, 262, 352, 654, 728, 780, 1569). Similarly, glibenclamide inhibits reactive hyperemia induced by 30 s occlusion in isolated rat hearts (1302). Reactive hyperemia also was reduced by 30% after 5 min occlusion in pig hearts, *in vivo* (1605). In murine hearts, *in vitro*, glibenclamide inhibits reactive hyperemia induced by 15 s ischemia (1286), confirming earlier studies (1623).

Autoregulation of blood flow and K_{ATP} channels

Blood flow to organs like the brain and heart displays autoregulation: blood flow tends to remain relatively constant in the face of changes in blood pressure or organ perfusion pressure. K_{ATP} channels have been implicated in autoregulation in both the heart and brain. Dilation of small coronary arterioles in response to reductions in perfusion pressure in anesthetized dogs (termed microvascular autoregulation) was abolished by glibenclamide (780, 781). Similarly, coronary autoregulation of blood flow was abolished by glibenclamide in anesthetized dogs (1058). Dilation of rat pial arterioles induced by a reduction in perfusion pressure was also impaired by sulfonylureas such as glibenclamide and glipizide (616, 834). Similar results were reported for blood flow to the brainstem as well as autoregulatory diameter increases to reduced blood pressure in small branches off of the rat basilar artery (1422).

In contrast, it has been reported that glibenclamide does not inhibit coronary autoregulation in anesthetized dogs (1336). No clear explanation for the lack of effect in this study versus those mentioned earlier, in the same tissue are apparent.

Pathophysiology and K_{ATP} channels

Hypertension—A number of studies suggest that K_{ATP} channel function is reduced in models of hypertension. SMC relaxation induced by K_{ATP} channel agonists has been shown to be reduced in: aortas in two-kidney-one-clip hypertensive rats (1455); basilar arteries from SHRSP (758); mesenteric arteries from SHR (724); aortas from DOCA-salt hypertensive rats (474); mesenteric arteries from L-NAME-induced hypertensive rats (722); and mesenteric resistance arteries from hypertensive BPH mice (1373). Similarly, K_{ATP} channel-opener-induced vasodilation is reduced in the brains of SHRSP (1374) and in the kidney of SHR (739). In mesenteric arteries of hypertensive BPH mice, expression of K_{IR} 6.1 and SUR2B are reduced, as are currents through K_{ATP} channels in this model of hypertension (1373). Reduced currents through K_{ATP} channels have also been reported in mesenteric arteries from SHR (1103). Reversal of hypertension by administration of antihypertensives has been reported to restore K_{ATP} channel function (1103, 1374). These data suggest that hypertension is the cause of the downregulated K_{ATP} channel function observed in those models.

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However, there are several studies that indicate that K_{ATP} channel function is either not changed (141, 635, 779), or actually enhanced (452, 1014) in models of hypertension. The study by Blanco-Rivero et al. (141) is particularly interesting because these investigators found a significant reduction in the expression of mRNA and protein for K_{IR} 6.1 and SUR2B in vessels from SHR, and yet patch clamp studies revealed no reduction in K_{ATP} channel currents and no effect on pinacidil-induced relaxation (141). Thus, our understanding of the effects of hypertension on K_{ATP} channel expression and function is incomplete.

Obesity and the metabolic syndrome—K_{ATP} channel expression and function appear to be downregulated in animal models of obesity and the metabolic syndrome. Insulin-induced vasodilation of mesenteric arteries, which appears to be mediated by K_{ATP} channels, was abolished in vessels from fructose-fed rats, a model of the metabolic syndrome (1003). Dilation of middle cerebral arteries mediated by K_{ATP} channels also is impaired in this model of insulin resistance (384, 385). Similarly, K_{ATP} channel-mediated arteriolar vasodilation is impaired in obese Zucker rats (608, 910). In this model, exercise capacity is reduced, an effect that can be reproduced by inhibition of K_{ATP} channels in lean control animals. Reactivity to cromakalim in human internal mammary arteries from patients with type 2 diabetes is also depressed suggesting a similar down regulation of K_{ATP} channel function in humans (652). Consistent with down regulation of K_{ATP} channels in obesity/metabolic syndrome, chronic treatment with sulfonylureas does not significantly affect reactive hyperemia in forearms of patients with type 2 diabetes (1330), a response that is mediated, in part, by activation of K_{ATP} channels (85, 137).

The mechanisms responsible for the down regulation of K_{ATP} channel function in obesity and the metabolic syndrome are not clear. The decreased insulin-reactivity, mediated by K_{ATP} channels, in vessels from fructose-fed rats can be restored by block of endothelin-A receptors (1003), suggesting increased endothelial cell production of endothelin may contribute to the reduced K_{ATP} channel function in this model. In diet-induced obesity in rats, relaxation of aortas and mesenteric arteries to a K_{ATP} channel agonist, K_{ATP} channel currents in SMCs and mRNA and protein expression from these two vessels were reduced (397, 399). Expression of SUR2B also is down regulated (398). However, the mechanisms responsible for the reduced K_{ATP} channel function and expression was not addressed. Pinacidil-induced dilation is reduced in mesenteric arteries of obese SHR rats relative to non-obese SHR and WKY rats, and reactivity can be restored with rosiglitazone treatment (643). The reduced function of K_{ATP} channels in fructose-fed rats appears to be mediated by ROS (385). Also, obesity-induced decreases in K_{ATP} channel function in Obese Zucker rats are associated with increased vascular levels of ROS (910). Inhibition of NADPH oxidase with apocynin reduces ROS and improves K_{ATP} channel function in this model (910). Thus the down-regulation of K_{ATP} channel expression and function may be induced by an increase in ROS production in obesity and the metabolic syndrome.

In contrast to studies showing decreased function and expression of K_{ATP} channels in models of obesity, adipose tissue in Ob^{-}/Ob^{-} mice releases substances that activate vascular SMC K_{ATP} channels, reducing basal vascular tone and vasodilator capacity (i.e., the vessels are already dilated, therefore the magnitude of any additional dilation is blunted) (1559).

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Also, it has been shown that hypercholesterolemia does not impair K_{ATP} channel-mediated vasodilation in the mesenteric bed of rabbits (1221). These data suggest that there are experimental model-dependent differences in the impact of obesity on vascular K_{ATP} channel function.

Aging—There is limited information concerning the impact of aging on the expression and function of vascular K_{ATP} channels. Diazoxide-induced increases in muscle blood flow are reduced in senescent Fischer 344 rats (653). Similarly, levcromakalim-induced dilation of small branches off of the basilar artery was impaired in aged Sprague-Dawley rats (1423).

Diabetes—Type 1 diabetes is also associated with a decrease in vascular K_{ATP} channel function. Streptozotocin-induced diabetes in rats impairs K_{ATP} channel agonist-induced relaxation or dilation in: aortas (725), pial arterioles (969), basilar arteries (968), and the coronary circulation (162). In addition, there are decreased basal and pinacidil-induced K_{IR} channel currents in aortic SMCs from streptozotocin-induced diabetic mice (851). Pinacidil-induced dilation was also impaired in mesenteric arteries and in the coronary circulation of the diabetic mice (851). Relaxation of human mesenteric arteries to cromakalim is impaired when exposed to elevated D-glucose (20 mM) (752). Also, hypoxia-induced dilation of human coronary arterioles is reduced due to decreased function of K_{ATP} channels in vessels from diabetic patients (1013). Exposure of vascular SMCs to elevated extracellular glucose impairs isoflurane-induced activation of K_{ATP} channels (738). The reduced vascular K_{ATP} channel function in streptozotocin-induced diabetic mice appears to result from increased S-glutathionylation of K_{IR} 6.1 in this model of type 1 diabetes (851). Previous studies have shown that S-glutathionylation of K_{IR} 6.1 at cysteine 176 induced by oxidative stress inhibits K_{ATP} channel function (1590, 1591). Treatment with the antioxidant MnTBAP restores K_{ATP} channel function in coronary arteries from human diabetic patients (1013), consistent with a role of ROS. High glucose-induced inhibition of K_{ATP} channel function in human mesenteric artery SMCs can be reversed by peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, which have antioxidant effects (752). In this same system, high glucose has been demonstrated to inhibit K_{ATP} channel function through increased NADPH oxidase activity and production of superoxide anions by a mechanism involving phosphatidylinositol 3-kinase (753). It has also been shown that long-term exposure to methyl glyoxal, an oxidant species produced during hyperglycemia, leads to down regulation of the expression (protein and mRNA) and function of K_{ATP} channels (1584) due to microRNA-mediated decreases in the expression of SUR2B (864). High glucose-induced activation of PKC, independent from ROS, has been proposed as another mechanism of downregulation of K_{ATP} channel function in vascular SMCs (738).

In contrast to the studies showing depressed K_{ATP} channel function in diabetes, it was shown that cromakalim-induced relaxation was enhanced in mesenteric resistance arteries from streptozotocin-induced diabetic SHR and WKY rats (724). Also, Lemakalim-induced relaxation of aortas and vasodilation of the mesenteric vascular bed were unaffected in streptozotocin-treated rats, despite depression of responses in the coronary circulation (162). Alloxan-induced diabetes in dogs or hyperglycemia increases aprikalim-induced dilation of coronary arterioles, although ischemia-induced dilation, which is mediated by K_{ATP}

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channels, is depressed (742). Also, in contrast to normal dogs, K_{ATP} channels contributed significantly to the local regulation of coronary blood flow during exercise (1440), suggesting increased, rather than decreased K_{ATP} channel function in this model of diabetes. An explanation for these results is not apparent, but could relate to the degree or duration of diabetes.

Other disease states—Perfusion of hearts with cardioplegic solutions results in a postcardioplegia-induced coronary hyperemia (1493). In pigs, this hyperemia can be inhibited by glibenclamide, suggesting a role for K_{ATP} channels (1493).

Global cerebral ischemia (91) and traumatic brain injury (61, 62, 735) impair vasodilation of the cerebral circulation by K_{ATP} channel agonists. In traumatic brain injury, the reduced K_{ATP} channel function has been proposed to result from a process involving elevated endothelin (735) production or release of vasopressin (62), activation of PKC and the production of superoxide anions (61, 62, 735) through a mechanism involving tyrosine kinase and ERK (1219).

In contrast to the down-regulation of K_{ATP} channel function that is observed in hypertension, obesity, the metabolic syndrome and diabetes, K_{ATP} channel function appears to be enhanced in models of heart failure (686, 1424, 1573) and subarachnoid hemorrhage (1318). However, the mechanisms responsible for the upregulated function have not been explored.

Sepsis represents another pathology in which vascular K_{ATP} channel function is upregulated. It was shown that K_{ATP} channels mediate, to a large extent, the hypotension that occurs in sepsis (813), that glibenclamide can reverse this hypotension, that cardiovascular function can be improved by block of K_{ATP} channels (1245) and that lipopolysaccharide stimulates vascular SMC expression of K_{IR} 6.1 and SUR2B augmenting K_{ATP} channel function via Nfkappa B signaling (1292). K_{ATP} channels are also likely activated by the lactic acidosis that is a hallmark of septic shock (813). However, this knowledge has not translated into clinical practice. Oral glibenclamide (10–30 mg enteral), at a therapeutic dose used to treat hyperglycemia, did not restore blood pressure or reduce norepinephrine requirement in septic patients (1027, 1498). However, these glibenclamide doses are much lower than required to block vascular K_{ATP} channels in sepsis (182). Also, early treatment with TEA (to block BK_{Ca} channels), but not glibenclamide improves cardiovascular function and organ damage in sepsis (1327). This is likely because K_{ATP} channels in vascular SMCs are protective: induction of sepsis is lethal in animals with knockout of K_{IR} 6.1 with a major effect mediated by K_{ATP} channels in the coronary circulation (729).

Ryanodine Receptors

Discovery of RyRs

RyRs are the largest known ion channel proteins (1457, 1577, 1617). They derive their name from the alkaloid, ryanodine, produced by the Columbian flowering shrub, *Ryania speciosa* (1212). Ryanodine was originally isolated and characterized for its insecticidal properties (1212), in which it produced paralysis, a transient increase in O_2 consumption and ultimately death (568). Skeletal muscle paralysis induced by ryanodine was subsequently

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demonstrated in vertebrates, including mammals (376), with the contraction process in the muscle identified as the site of action (376), but no effect on the muscle membrane or the activity of the contractile proteins (144). Blum et al. (144) speculated that ryanodine acted by combining with a substance that couples excitation of the muscle membrane with activation of the contractile proteins; the first hint of the existence of RyRs.

Ryanodine was shown to increase both the uptake and release of Ca^{2+} from skeletal muscle (17), and in particular, to increase the efflux of Ca^{2+} from the sarcoplasmic reticulum (394, 395). In parallel, Ca^{2+} release from the terminal cisternae in skeletal muscle was established as the trigger for muscle contraction [see (381) for a review]. Subsequently, specific binding of ryanodine to terminal cisternae membrane vesicles of skeletal and cardiac muscle was reported (432, 1157), with the binding sites named Ca^{2+}-RyRs (1157). Proteins from these membranes could be inserted into lipid bilayers to reconstitute a functional Ca^{2+} channel (1314). This knowledge then was used to isolate and purify RyRs from both skeletal and cardiac muscle (636, 649, 650, 811, 1232), to show that RyRs formed functional Ca^{2+} release channels when incorporated into planer lipid bi-layers (636, 811, 1045) and to demonstrate that these channels were ryanodine-sensitive (1045). The lipid bilayer studies also showed that low concentrations of ryanodine locked the channels into a subconductance state, allowing leak of Ca^{2+} from the sarcoplasmic reticulum, consistent with the vesicle studies (394, 395), while high concentrations of ryanodine blocked the channel (1045).

Structure of RyRs

RyRs are composed of a homo-tetramer of ~560 kDa subunits that form ryanodine-sensitive, Ca^{2+}-selective channels in the membrane of the ER (1577, 1617). The ion conductive portion of the RyR is located in the C-terminal portion of the peptide and arises from association of 6 transmembrane spanning domains (S1–S6) from each of the four subunits, much like the structure of K_V channels, with a loop between S5 and S6 (P-loop), and S6 contributing to the ion conducting pore of the channel (1577, 1617) (Fig. 2). The P-loop and S6 contain a large number of negatively charged residues contributing to the high Ca^{2+} conductance of RyRs [~120 pS (346, 1617)]. Large N-terminal and smaller C-terminal domains are located in the cell cytoplasm and constitute the bulk of the mass of the protein (~80%) and contain the Ca^{2+} sensor (responsible for Ca^{2+}-induced-Ca^{2+} release), binding sites for a large number of interacting protein binding partners, and phosphorylation sites for regulation by protein kinases (1100, 1457). The N-terminal domain of each subunit consists of two β-trefoil domains (domains A and B) and a group of α-helices (domain C (1441) or N-Sol (1617)) that interact with each other through a number of hydrophilic interfaces (1441). These three domains form a large vestibule of the channel pore, and disease-related mutations in a number of residues in these domains have been identified (1441). The bulk (56%) of the remainder of the cytosolic domain consists of a scaffold of α-solenoid repeats with three large SPRY domains [domains found in SplA kinase and RyRs (1577)], two pairs of RyR repeats, the calstabin (FK506 binding protein, FKBP)-binding domain and an EF-hand pair, which is the presumed Ca^{2+}-binding domain (1577, 1617). The most proximal portion of the α-solenoid repeats (termed the core solenoid by Zalk et al.) contains the EF-hand pair and interacts with the C-terminus of the channel (1617). The RyR domains contain presumed regulatory phosphorylation sites (1577). This large flexible domain structure

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serves both as a scaffold for recruitment of regulatory proteins to the channel and to allow coupling of conformational changes induced by ligand binding and protein phosphorylation and other post-translational modifications (1617). A cytosolic loop connecting segments 2 and 3 of the pore domain appears to interact with the Ca^{2+}-sensing EF-hand domain providing a means to couple Ca^{2+} binding with gating of the RyR Ca^{2+} channel (377, 1617).

RyR isoforms

There are three isoforms of RyRs (RyR1, RyR2, and RyR3) that are the products of three genes (818) with high sequence homology (66% between RyR1 and RyR2, 67% between RyR1 and RyR3, and 70% between RyR2 and RyR3) (538, 1377, 1656). Sequence differences among the three isoforms are located in three regions, termed D1, D2, and D3 that are located in the large N-terminal cytoplasmic domain and which likely account for differences in the function of these isoforms (818, 1456).

RyR expression

It was initially shown that skeletal muscle cells express predominantly RyR1, the heart predominantly RyR2, and the brain and other cells in the body, RyR3 (477, 831, 1196). However, subsequent studies have demonstrated expression and function of all three isoforms around the body (477, 921, 1618).

Vascular SMCs display regional heterogeneity in the expression of RyR isoforms (1241, 1451, 1453, 1527, 1528, 1587). Expression of predominantly RyR2 was found in rat aorta and pulmonary arteries (1587). Similarly, in SMCs from posterior, middle or anterior cerebral arteries, RyR2 message and protein were more highly expressed than RyR1 or RyR3 (1451). Studies of SMCs isolated from murine skeletal muscle resistance arteries and arterioles also demonstrated predominant expression of RyR2 (1527). However, in these SMCs, RyR3 was expressed at a much lower level, and RyR1 was not detected (1527). In contrast, Salomone et al. (1241), found expression of only RyR3, but not RyR1 or RyR2 in basilar artery SMCs. These data suggest that there are significant regional differences in RyR isoform expression. Consistent with this hypothesis, it was shown that rat pulmonary conduit and mesenteric arteries express RyR1 and RyR2 with little expression of RyR3 (1639). However, all three isoforms were expressed at similar levels in pulmonary resistance arteries. In a separate study of mesenteric resistance arteries, RyR1 and RyR3 expression were greater than RyR2 (857).

The expression of RyR isoforms also may change during proliferation as it has been shown that cultured rat aortic SMCs, express predominantly RyR3 followed by RyR2 and RyR1 (1453), whereas RyR2 predominated in freshly isolated tissue (1587). Consistent with the idea of isoform expression heterogeneity, studies of primary cultures of portal vein SMCs by Coussin et al. (278) showed similar expression of RyR1 and RyR2, with lower RyR3 expression. Thus, in addition to regional heterogeneity in isoform expression, proliferating SMCs likely express different isoforms of RyRs suggesting varied roles for the three RyR isoforms.

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RyR alternative splicing

The complexity of the pattern of expression of RyR isoforms is also increased by alternative splicing that may contribute to their functional heterogeneity in the vasculature. RyR1 has two splice variants, ASI and ASII (Alternative Splice sites I and II) (455). Expression of these variants appears to increase RyR1 activity (750, 751). Alternative splicing of RyR3 has been detected in vascular SMCs (837, 955, 1015). One of these RyR variants (AS-8a, with a deletion in exon 8) is unique to SMCs and leads to expression of an RyR with decreased function (300, 706). Heterodimerization of the AS8a with normal RyR3 may decrease channel activity (706).

Regulation of RyR function

Calcium—Cytosolic Ca^{2+} displays a bell-shaped concentration-response relationship with low concentrations (0.1–10 μmol/L) activating the channel and higher concentrations inhibiting channel activity (232, 275, 543, 545, 700, 707, 825, 1152, 1428, 1457). RyR1 is inhibited by cytosolic Ca^{2+} concentrations of 1 mmol/L or higher (545, 707). RyR2 and RyR3 also can be inhibited by Ca^{2+}, but at even higher concentrations (229, 1260). The binding site for Ca^{2+}-dependent gating of RyRs is presumably mediated via the EF-hand domain located in the proximal α-solenoid domain of the N-terminus, as noted above (377, 1617). Ca^{2+}-dependent inhibition of the channel likely involves several lower affinity Ca^{2+}-binding sites on the protein (818).

The Ca^{2+} concentration in the lumen of the ER also impacts the function of RyRs (233, 425, 525, 825). Increased Ca^{2+} load in ER stores leads to increased opening of RyRs (233, 425, 525). Released Ca^{2+} may interact with cytosolic Ca^{2+} activation sites to increase RyR activity (1428). In addition, the helix bundle-crossing region, part of the proposed Ca^{2+} gate in RyR2, has been shown to be essential for luminal Ca^{2+} sensing (233). Finally, luminal Ca^{2+} may interact with Ca^{2+}-binding proteins within the ER such as calsequestrin to modulate RyR activity (526).

Phosphorylation—Examination of the amino acid sequences of RyRs reveal a large number of potential phosphorylation sites (425, 545, 992, 1100, 1375, 1618). Consensus sequences for PKA, CamKII, and PKG are present (347, 992, 1618). However, PKA and CamKII appear to be the most important (347, 992, 1618) (Fig. 9). Both kinases have specific anchoring regions on RyR (98, 954). In addition, Protein Phosphatase 1 (PP1) associates both with RyR1 and RyR2, Protein Phosphatase 2A (PP2A) associates with RyR2 and PP2B (calcineurin) associates with RyR1 (992). The kinases and phosphatases are targeted to RyRs by anchoring proteins: PKA and phosphodiesterase 4D3 via mAKAP, PP1 via sinophilin, PP2A via PR130 (aPP2A targeting protein) (1618), and PP2B (calcineurin) via mAKAP (96).

The functional effects of RyR phosphorylation remain a matter of debate (992, 1100). Most studies suggest that phosphorylation by CamKII and PKA leads to increased RyR activity (425, 1508, 1541, 1618) (Fig. 9). However, contrary results have been reported (115, 355, 921). Hyperphosphorylation (phosphorylation of all four RyR subunits) of RyR2 has been reported to cause dissociation of FKBP12.6, a RyR-associated protein, resulting in leaky

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channel function (1506, 1507). However, acute phosphorylation of RyR2 has been reported to increase activity (535), decrease channel opening (1452), or produce no change in RyR Ca^{2+} handling (856). How RyR phosphorylation affects vascular SMC function has not been established.

Calmodulin, Sorcin, and S100A1—The Ca^{2+} binding protein, calmodulin (248), associates with RyRs in the proximal portion of the N-terminal domain near the transmembrane spanning domains (1484). High-micromolar, concentrations of Ca^{2+} increase calmodulin binding to RyRs, and RyR inhibition (thus limiting CICR at high Ca^{2+}), whereas nanomolar Ca^{2+} concentrations decrease binding and increase RyR activity (425, 545). RyR1 and RyR3 are more sensitive to activation by calmodulin in the presence of low Ca^{2+} concentrations, while Ca^{2+}-calmodulin-dependent inhibition of RyR2 occurs at lower Ca^{2+} concentrations relative to RyR1 or RyR3 (442, 443) (Fig. 9).

RyRs also can be modulated by another Ca^{2+}-binding protein, Sorcin, which inhibits RyRs at high-micromolar concentration of Ca^{2+} (347) (Fig. 9). Sorcin immunoprecipitates with RyRs in cardiac muscle (999). In rat aortic and cerebral artery SMCs, Sorcin expression is higher and RyR2 expression is lower than what is observed in cardiac myocytes (1223). They proposed an increased role for Sorcin-RyR interaction in vascular SMCs, confirmed by a lower frequency of RyR-mediated Ca^{2+} sparks (1223). Sorcin has also been proposed to prevent the propagation of Ca^{2+} sparks to adjacent groups of RyRs by detecting Ca^{2+} released from a spark site, binding to nearby RyRs, and inhibiting Ca^{2+} spark propagation (410, 411).

The protein S100A1, another EF-hand-containing protein, also interacts with RyRs (1177, 1427), with a functional outcome distinct from calmodulin or Sorcin. In the presence of Ca^{2+}, S100A1 increases RyR activity, promoting Ca^{2+} release (1427) (Fig. 9). This process may involve competition of S100A1 with calmodulin (1177). Vascular SMCs express S100A1 (939), however, the function of this protein in the regulation of vascular SMC RyRs has not been explored.

FKBP12/FKBP12.6—FKBPs are a family of 20 immunophillins named because they serve as binding sites for the immunosuppressant, FK506 (922). Two of this family, FKBP12 and FKBP12.6 (numbered according to molecular mass and also referred to as calstabin 1 and 2, respectively), regulate the function of RyRs (14, 224, 922). FKBPs bind near the interface among the SPRY1, SPRY2 and linking α-solenoid region 2 domains of the N-terminus (1617). FKBPs bind to each RyR monomer with such high affinity that the two proteins co-purify (943). It has been proposed that binding of FKBPs to RyRs clamps SPRY2 and α-solenoid 1 domains together restricting their motion, and hence, decreasing channel activity (377) (Fig. 9). All three RyR isoforms can interact with both FKBP12 and FKBP12.6 (943). However, RyR2 preferentially binds FKBP12.6, and RyR1 and RyR3 preferentially bind FKBP12 (943). For RyR1, removal of FKBP12 causes increased channel activity (425, 922). However, less is known about the regulation of RyR2 and RyR3 by FKBPs (425, 922). The physiological significance of the interaction between FKBPs and RyRs has not fully emerged. Mutations in RyR1 related to malignant hyperthermia are near the FKBP-binding site (224), suggesting that the RyR1 dysfunction observed in this disease

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could be related to altered RyR-FKBP interactions. In heart failure, it has been proposed that displacement of FKBP12.6 from the RyR2 due to hyperphosphorylation of the channel increasing RyR activity resulting in leak of Ca^{2+} from the ER (115, 355). Overexpression of FKBP12 in cardiac myocytes decreases the amplitude and duration of Ca^{2+} sparks (702). Conversely, pharmacological dissociation of FKBPs from RyRs in bladder SMCs leads to increased Ca^{2+} spark amplitude and frequency (971). Increased expression of FKBP12.6 in cerebral arteries has been proposed to be the cause of decreased expression and activity of RyR2 (775).

However, there appears to be regional and perhaps species differences in the role played by FKBPs in the regulation of SMC function. In pulmonary artery SMCs, FKBP12.6 associates with RyR2, but not RyR1 or RyR3 (1637). FKBP12 associates with and modulates the activity of RyR2 in guinea pig colonic SMCs (924). However, although FKBP12 is expressed in aortic SMCs, it does not associate with RyR3 (the major isoform expressed in this tissue) and does not modulate RyR3 function (923, 924). Similarly, RyR function in porcine coronary artery SMCs (1597) and bovine renal, coronary or mesenteric arteries (383) appears not to be modulated by FKBPs. In contrast, FKBPs appear to attenuate RyR function in guinea pig bladder (1513) and portal vein (925) SMCs independent from calcineurin (see later). An inhibitory role for FKBPs have also been proposed in the regulation of RyR function in rat aortic SMCs (234). Thus, there appears to be regional and likely species dependent differences in role played by FKBPs in the regulation of RyR function.

It should be noted that FKBPs also serve other actions that have the potential to modulate the function of RyRs independent from effects mediated by direct binding of FKBPs to RyRs (922). The drug FK506 (Tacrolimus) binds to FKBPs resulting in dissociation of the FK506-FKBP complex from RyRs. The FK506-FKBP complex then inhibits the Ca^{2+}-calmodulin-dependent phosphatase, calcineurin, which is responsible for the immunosuppressive effects of FK506 (922). Calcineurin may be tethered to RyRs by FKBPs targeting this phosphatase to RyRs, and providing a mechanism for modulation of RyR function via dephosphorylation (922). However, in SMCs, some studies suggest that calcineurin does not modulate RyR function (922, 924, 925). In contrast, inhibition of calcineurin or its genetic knockout inhibits RyR1 function in murine airway smooth SMCs (1256). Thus, there may be regional or species differences in the role played by calcineurin in the modulation of SMC RyR function.

The immunosuppressant drug, rapamycin, also results in dissociation of FKBPs from RyRs, but inhibits the function of the protein kinase, mammalian target of rapamycin (mTOR) (922). This pathway also does not appear to contribute to acute modulation of RyR function in SMCs (922). However, the mTOR pathway may participate in more long-term modulation of RyR expression and function (1031).

Cyclic adenosine diphosphate ribose and RyRs—Cyclic adenosine diphosphate ribose (cADPR) has been proposed to modulate RyR function in vascular SMCs (390). This second messenger is synthesized by SMC microsomes from coronary, renal and pulmonary arteries (390). However, there seems to be substantial regional heterogeneity: in the rabbit,

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pulmonary artery SMCs synthesize more than tenfold higher levels of cADPR compared to aortic or mesenteric resistance artery SMCs (1535). Similarly, in rat kidneys, preglomerular vessels synthesize much more cADPR than do postglomerular vessels (861). Calcium release induced from intracellular stores by cADPR has been demonstrated in rabbit small intestine longitudinal (but not circular) SMCs (796), bovine coronary SMCs (1610), rabbit (1535) and rat (148) pulmonary artery SMCs, and renal microvessels (861). Dialysis of rat tail artery SMCs with cADPR increases the frequency of RyR-dependent STOCs (243). This second messenger also has been shown to activate bovine coronary artery RyRs reconstituted into lipid bilayers (1386). The effects of cADPR on Ca^{2+} release does not appear to result from direct binding of this messenger to RyRs (390). Because cADPR activates RyRs in bovine coronary SMCs only when FKBP12.6 is associated with the RyR (1386), FKBP12.6 has been proposed as the receptor for cADPR, or at least to be required for its action on RyRs. This hypothesis is supported by studies in renal microvessels (1396) and murine bladder SMCs (1640). In contrast to the studies supporting a role for cADPR in modulating RyR function, studies in guinea pig colonic SMC found no effect of cADPR on RyR function even in the presence of FKBP12.6 (167). Instead, effects on removal of Ca^{2+} from the cytosol were reported (167). However, these studies have not been confirmed.

It has been proposed that cADPR-RyR signaling may be involved in the mechanism of action of vasodilators that act through both the cAMP and cGMP signaling cascades, via effects on Ca^{2+} sparks and RyR-dependent STOCs (390). However, block of cADPR signaling has also been shown to cause vasodilation, rather than the predicted vasoconstriction if this hypothesis were correct, and to not affect vasodilation induced by dilators that act through the cAMP-signaling cascade, data that also are not consistent with this hypothesis (469).

Scaffolding and anchoring proteins—There are several scaffolding and anchoring proteins that may contribute to the regulation of the RyR function (224). The scaffolding protein Homer binds to proline-rich sequences of proteins, and couples membrane receptors to intracellular Ca^{2+} stores (347). Homer interacts with RyR1, but not RyR2 or RyR3, which lack the consensus sequence for this interaction (347). In skeletal muscle, interaction of Homer with RyR1 increases channel activity (418). However, it is not known if a similar interaction occurs in SMCs.

Anchoring proteins, such as AKAPs tether PKA to RyRs (992). In cardiac muscle, AKAP immunoprecipitates with RyR2, suggesting a close association (953). In skeletal muscle, mAKAP targets PKA to RyR1, with phosphorylation increasing RyR1 activity (1225). The expression and function of anchoring proteins in the regulation of RyR function in vascular SMCs has not been explored.

Oxidation and nitrosylation—RyRs are sensitive to the redox status of cells because they have more than 100 cysteine residues in each RyR monomer (347, 992). Oxidation of exposed cysteines has been shown to increase RyR activity in RyR1 and RyR2 (345, 347, 357, 358, 527), likely by altering interactions with RyR-associated proteins (1632). For example, in diseases characterized by contractile dysfunction and muscle weakness such as heart failure, muscular dystrophy and age-related sarcopenia, RyR oxidation results in

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dissociation of FKBP12 and/or FKBP12.6 from the RyR, Ca^{2+} leak and muscle dysfunction (1195).

Nitric oxide also can interact directly with RyRs resulting in S-nitrosylation (992). Low levels of S-nitrosylation appear to activate RyR1, whereas high levels of S-nitrosylation appear to be inhibitory (992). In contrast, RyR2 requires S-nitrosoglutathionylation via peroxynitrite (992).

Intracellular ion channels and RyR function—Release of Ca^{2+} from the SR results in loss of positive charge from ER stores and development of a negative potential across the ER membrane, with the opposite occurring when Ca^{2+} is pumped back into the SR (1475). To counter this charge imbalance, there is a flux of cations (principally K^+) through Trimeric Intracellular Cation-selective (TRIC) channels (1475). There are two isoforms of TRIC channels, TRIC-A and TRIC-B (1475). Knockout of TRIC-A compromises RyR1 function in skeletal muscle (1475) and in vascular SMC (1575).

Another ER-membrane ion channel, TRPP1 interacts with and inhibits the function of RyR2 (5, 52). The N-terminus of TRPP1 binds to RyR2, and the C-terminus binds only when the RyR2 are in an open state (52). However, the mechanism of inhibition of RyR2 function has not been established.

Pharmacology of RyRs

The pharmacology of RyRs is outlined in Table 3. As noted above, ryanodine acts as both an agonist, and a blocker of RyRs, dependent on the concentration (1657). At concentrations less than 1 μmol/L, ryanodine locks the RyR into a subconductance state, releasing Ca^{2+} from the ER that can lead to store depletion (1657). At concentrations above 10 μmol/L, ryanodine blocks RyRs (1657). Tetracaine also blocks RyRs, but does not lead to store depletion (1657). However, this local anesthetic also has a number of off-target effects including block of vascular SMC K^+ channels that limits its usefulness in whole tissue studies (573). The RyR agonist, caffeine also has significant off-target effects such as phosphodiesterase inhibition that also make its use in whole tissue or *in vivo* studies problematic (1528).

RyR function in vascular SMCs

In skeletal and cardiac muscle, RyRs amplify signals from other ion channels and importantly contribute to the increase in intracellular Ca^{2+} that triggers muscle contraction. The function of RyRs in SMCs is more variable and less well understood (269). In some vessels, RyRs amplify Ca^{2+} signals generated by other ion channels contributing to increases in intracellular Ca^{2+} and promoting vasoconstriction. For example, Ca^{2+}-induced-Ca^{2+} release (CICR) stimulated by Ca^{2+} influx through L-type VGCCs (269, 493, 590, 638, 639) or due to Ca^{2+} release through IP_3Rs (142, 149) has been reported in some SMCs. Furthermore, in some blood vessels RyRs contribute to IP_3R-dependent Ca^{2+} waves that are excitatory and promote vasoconstriction (678, 1035, 1036, 1527, 1528) (Fig. 4, see IP_3R Section for more on this topic). However, unlike cardiac or skeletal muscle, RyR-dependent CICR may not be essential for vasoconstriction, because many SMCs contract at cytosolic

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Ca^{2+} concentrations lower than required to activate RyR-mediated CICR (512). The variability in RyR function likely results from differences in expression and localization of RyRs in SMCs in various blood vessels (1241, 1451, 1453, 1528, 1587).

Role of Ca^{2+} sparks in SMCs—RyRs contribute to at least two types of Ca^{2+} signaling events in vascular SMCs: Ca^{2+} waves, that will be discussed further in the IP_3R section, and Ca^{2+} sparks, which have already been mentioned in the section on BK_{Ca} channels, above. Calcium sparks result from the rapid opening of a small group of RyRs in the ER, leading to transient, focal increases in subplasmalemmal Ca^{2+} concentrations, without a significant effect on global Ca^{2+} levels (388). In skeletal (760) and cardiac muscle (1328), and in some SMCs (81, 297, 298, 415, 416, 804, 1438), RyR-dependent Ca^{2+} sparks function in a positive-feedback manner that is critical for excitation-contraction coupling (197, 235). In some vascular SMCs, Ca^{2+} sparks also may activate Ca^{2+}-activated Cl^- (Cl_{Ca}) channels to produce spontaneous transient inward currents (STICs) (235). These currents depolarize cells, activating L-type VGCC and promoting vasoconstriction (1650).

In contrast, in some vascular SMCs, RyR-mediated Ca^{2+} sparks importantly participate in a negative-feedback loop that contributes to the regulation of myogenic tone (235, 683, 1071) (Fig. 4). As covered in the BK_{Ca} channel Section, this negative-feedback mechanism involves Ca^{2+} spark-dependent activation of overlying BK_{Ca} channels to produce STOCs, membrane hyperpolarization, deactivation of L-type VGCCs and reduced myogenic tone (235, 683, 1071).

In some arterioles in the microcirculation, RyRs appear to be silent at rest and do not contribute to the regulation of myogenic tone. In first-order rat cremaster arterioles (1589), second-order hamster (1528) and mouse (1527) cremaster arterioles, rat cerebral penetrating arterioles at rest (301), and ureteral arterioles (160), RyRs do not seem to participate in the negative-feedback regulation of myogenic tone. In cerebral penetrating arterioles, low pH stimulates generation of Ca^{2+} sparks, STOCs and BK_{Ca} channel-mediated vasodilation (301).

RyR isoforms and Ca^{2+} sparks—Differences in the pattern of expression of RyR isoforms may explain variation in the occurrence and properties of Ca^{2+} sparks (388). For example, RyR1 and RyR2 are required for Ca^{2+} sparks (278, 866, 1008), while the function of RyR3 is unclear (388). In rat portal vein, antisense knockdown showed Ca^{2+} sparks depend on expression of RyR1 and RyR2, whereas knockdown of RyR3 has no impact (278, 1008). However, silencing of RyR3 altered global Ca^{2+} levels in this model (278, 1008). In contrast, vascular SMCs from $RyR3^{(-/-)}$ mice display increased Ca^{2+} spark frequency, suggesting an inhibitory role for RyR3 (900). Consistent with this hypothesis, Ca^{2+} sparks were absent from murine cremaster arteriole SMCs which showed an elevated ratio of expression of RyR3/RyR2 relative to SMCs from upstream arteries that displayed Ca^{2+} sparks (1527).

Vasoconstrictors, RyRs and Ca^{2+} sparks—PKC activation contributes to myogenic tone in some blood vessels (597, 1113), and activation of PKC signaling can decrease the occurrence of Ca^{2+} sparks in some SMCs (153, 681, 896). In rat cerebral SMCs, UTP-

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induced decreases in Ca^{2+} spark frequency occur independent from the ER Ca^{2+} load suggesting a direct effect on RyR function (681). However, it has been shown that norepinephrine, which should activate PKC, stimulates Ca^{2+} sparks in guinea pig mesenteric SMCs (1179). Thus, there may be regional or species differences in the role played by PKC in modulating Ca^{2+} spark activity.

Vasodilators, RyRs and Ca^{2+} sparks—A number of vasodilators have been suggested to act, in part by activation of SMC RyRs leading to an increase in the frequency of Ca^{2+} sparks, increased activity of BK_{Ca} channels, membrane hyperpolarization, deactivation of VGCCs, reduced intracellular Ca^{2+} and vasodilation. Early studies showed that the adenylate cyclase activator, forskolin, increased Ca^{2+} spark frequency in SMCs isolated from rat basilar or coronary arteries and that vasodilation induced by forskolin could be substantially inhibited by ryanodine (1169) (Fig. 9). Similarly, adenosine in rat cerebral and coronary artery SMCs (1169), arginine vasopressin in rat retinal arteriolar SMCs (691) and pituitary adenylate cyclase activating polypeptide in rat cerebral artery SMCs (776) act via the cAMP-PKA signaling cascade to stimulate Ca^{2+} spark frequency (Fig. 9). The increase in Ca^{2+} spark frequency in these studies could be due to cAMP-PKA targeting either RyRs (992, 1100) or phospholamban (1306, 1521). Phosphorylation of phospholamban by PKA disinhibits the ER Ca^{2+} ATPase, SERCA, increasing Ca^{2+} in the lumen of the ER. Studies using phospholamban knockout mice revealed that the increase in Ca^{2+} spark frequency induced by forskolin appeared to be mainly mediated by cAMP-PKA-dependent phosphorylation of phospholamban (1521). This would increase the load of Ca^{2+} in the SR, which is known to increase the activity of RyRs and the frequency of Ca^{2+} sparks (241, 1651). It has also been proposed that the effects of cAMP-related vasodilators on Ca^{2+} sparks may be mediated through EPACs in SMCs from rat mesenteric arteries (1206) (Fig. 9).

Like the cAMP pathway, NO-dependent signaling via cGMP-dependent PKG also may increase RyR activity by increasing ER Ca^{2+} content and by sensitizing RyRs to Ca^{2+}-dependent activation (1169). NO also can directly S-nitrosylate RyR1 to increase RyR activity (1357), and other mechanisms of action have been proposed (992).

However, there are data that conflict with these early findings. Pucovský et al. (1179) found that in SMCs from guinea pig mesenteric arteries, high concentrations of the NO donors SNP (100 μmol/L) or SNAP (50 μmol/L) had no significant effect on Ca^{2+} spark frequency unless these agents were applied in the presence of norepinephrine, in which case a decrease in Ca^{2+} spark frequency was observed. The inhibition of Ca^{2+} spark activity appeared to be due to a direct effect of NO, because inhibition of guanylate cyclase did not block the effect (1179). Nitric oxide also has been shown to inhibit caffeine-induced Ca^{2+} transients in bovine coronary artery SMCs (868). It was suggested that NO inhibits ADP-ribosyl cyclase and cADPR formation to inhibit RyR function in these cells (1610). This effect also appeared to be a direct effect of NO. On the other hand, a lack of effect of NO on caffeine-induced Ca^{2+} transients also has been reported in rat aortic SMCs (701) suggesting no effect of NO on RyR function. Thus the effects of the NO and cGMP pathways on RyR function in vascular SMCs is far from clear.

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Hydrogen sulfide has been shown to increase Ca^{2+} spark frequency in SMCs from piglet cerebral arteries by increasing the Ca^{2+} load in the SR, a mechanism that contributes to the vasodilation induced by H_2S in this vessel (871). In rat mesenteric SMCs, H_2S increases Ca^{2+} spark frequency, but only in arteries with an intact endothelium suggesting an indirect effect in this system (675, 676).

RyRs and pathophysiology

Hypertension—Early studies found that caffeine-induced contraction of mesenteric resistance arteries (1033) and aortas (727) is increased in vessels from SHRSP versus WKY rats and that this is likely due to an increased Ca^{2+} load in the SR (727). RyR function also appears to be enhanced in SMCs from SHR versus WKY rats (276). However, no difference in the amplitude or frequency of Ca^{2+} sparks in cerebral artery SMCs from SHR versus WKY or Sprague-Dawley rats was reported (43). In angiotensin II-induced hypertension, Ca^{2+} spark frequency was unchanged, but Ca^{2+} spark amplitude was increased in SMCs from rat cerebral arteries (39). These data suggest that different causes of hypertension may have different effects on RyR function. There also may be regional differences, as increased expression of RyR2, increased Ca^{2+} spark frequency and increased function of RyRs were found that contribute to purinergic P2X receptor-mediated Ca^{2+} signaling in rat renal preglomerular arterial SMCs in SHR versus WKY (495).

Knockout of TRIC-A channels results in reduced Ca^{2+} spark frequency with no change in amplitude, leading to membrane depolarization due to less spark-dependent activation of BK_{Ca} channels (1575). This may contribute to the increased myogenic tone and hypertension in this mouse model and in humans with TRIC-A mutations (1575). Overexpression of TRIC-A results in hypotension and increased Ca^{2+} spark frequency (1390).

Maternal consumption of caffeine in rats results in decreased expression of RyR1 and RyR3 in mesenteric arteries of offspring, decreased frequency of STOCs (as a surrogate marker of Ca^{2+} sparks), membrane depolarization and increased vascular reactivity that correlates with increased pressor responses in the offspring (857). These changes may contribute to development of hypertension in these offspring as they age (857).

Aging—Expression of TRPP1 in the ER has a stimulatory effect on RyR function (5). Aging is associated with a decrease in the function of RyRs and reduced modulation of RyRs by TRPP1, which is associated with no change in the apparent expression of TRPP1 (5).

Diabetes—The effects of diabetes on RyR expression and function are not clear (421). For example, no change in RyR function was reported in mesenteric arteries from streptozotocin-induced diabetic rats (1505). In tail arteries from this same model, an increase in RyR function was found (1379). Aortic SMCs from two models of diabetes in rats, and high glucose exposure of A7R5 cells resulted in an increase in RyR protein expression and redistribution of RyRs from SR to nuclear membranes (1274).

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However, decreased expression of RyR protein in aortic SMCs from streptozotocin-induced diabetic rats was reported (918). A reduced release of Ca^{2+} induced by ryanodine also was observed in these cells in contrast to what was reported by (1505). In cerebrovascular SMCs from male diabetic *db/db* mice, RyR expression also is reduced and is accompanied by a modest reduction in the amplitude, duration and mean rise time of the sparks with no change in frequency (1222). While Ca^{2+} spark frequency was unchanged, STOC frequency and amplitude were reduced due to reduced coupling of sparks to STOCs (1222). In cerebrovascular SMCs from female *db/db* mice, while the frequency of Ca^{2+} sparks was reduced, there was no difference in other spark properties and no difference in properties of STOCs indicating that there are likely gender differences in the effects of diabetes on RyR function in this model of type 2 diabetes (1222). Thus, there is not a clear view of how diabetes influences the expression and function of RyRs and how this contributes to the vascular pathologies associated with this disease. Little is also known of the mechanisms responsible for the changes in RyRs that have been observed. In cardiac myocytes from rats on a high-fructose diet, ROS-activated CamKII leads to increased phosphorylation of RyR2 and an increase in RyR2 activity that may contribute to arrhythmias in the model (1322). It is not known if a similar mechanism is operational in vascular SMCs.

Subarachnoid hemorrhage—Subarachnoid hemorrhage (SAH) results in substantial increases in vascular tone that can progress into vasospasm in large arteries, resistance arteries and arterioles (775). In a rabbit model of SAH, there was a reduction in the frequency of Ca^{2+} sparks in SMCs isolated from posterior cerebral and cerebellar arteries in this model that resulted in a decrease in the frequency of BK_{Ca} channel STOCs (775). Associated with this change in RyR function, there was a reduction in the expression (message and protein) of RyR2 and an increase in the expression of FKBP12.6 (775). It was proposed that the substantially increased ratio of FKBP12.6 to RyR2 was responsible for the reduced frequency of Ca^{2+} sparks, and that via reduced activation of BK_{Ca} channels, the reduction in RyR channel function contributes to the increased vascular tone observed after SAH (775). However, the mechanism responsible for the altered expression of RyR2 and FKBP12.6 were not established, and the contribution of the altered RyR2 function to the changes in cerebral resistance artery tone after SAH is not known.

Inositol-1,4,5-triphosphate Receptors

Discovery of IP_3Rs

Release of Ca^{2+} from nonmitochondrial stores by IP_3 was first described in pancreatic acinar cells (1344). Subsequent studies identified a similar process in a variety of cells (124, 1395) including vascular SMCs (1350), and it was proposed that IP_3 bound to a receptor in the membrane of the ER to stimulate Ca^{2+} release (124). Subsequently, a 260 kD IP_3R was isolated and purified from rat cerebellum (1361), which, when reconstituted into lipid bi-layer vesicles, allowed IP_3-dependent Ca^{2+} flux (423). The full length IP_3R1 was then cloned from mouse cerebellum (454) and subsequent studies showed that there are three IP_3R family members (IP_3R1, IP_3R2, and IP_3R3), as outlined later (434).

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Structure of IP_3Rs

IP_3Rs are homotetramers of large subunits (~310 kD) that form Ca^{2+} release channels in the membrane of the ER (434). Like RyRs (1280, 1282), IP_3Rs consist of a long, cytoplasmic N-terminus, 6 transmembrane domains (S1–S6) that form the ion conductive portion of the channel, followed by a short cytoplasmic C-terminal domain (145). The ion conductive pore is likely formed by transmembrane S5 and S6, and the P-loop between these segments similar to RyRs (145) (Fig. 2). Each IP_3R monomer contains one binding site for IP_3 that is located toward the N-terminus of each monomer and is referred to as the IP_3-binding core (IBC) (434, 1280, 1282, 1395). Each IBC consists of α- and β-domains; these interact with the 5- and 4-phosphate groups of IP_3, respectively, and lead to a conformational change that gates the channels open (1280, 1282, 1395). At the N-terminus is a suppressor domain (SD) that interacts with, and stabilizes the IBC in the absence of ligand, and is essential for channel gating (1280, 1282, 1395). Peptide loops within the IBC β-domain and the SD domain of each monomer interact with adjacent monomers, and stabilize the IP_3R in the closed state in the absence of ligands (1280, 1282, 1395). This configuration of the SD, α- and β-domains of IP_3R1s is similar to the A, B, and C domains of RyR1 (1280, 1282). Between the IBC and the transmembrane spanning domains is a long regulatory domain that contains sites for interaction with a number of proteins including TRPC coupling domains, putative binding sites for Ca^{2+} and ATP and consensus sequences for phosphorylation by several protein kinases (434).

IP_3R isoforms and expression

Mammalian IP_3Rs exist in three isoforms (IP_3R1-IP_3R3) that are the products of three genes (434). The isoforms display approximately 60% to 80% sequence homology, with the pore and ligand-binding regions being highly conserved (933). The majority of tissues, including vascular SMCs, express multiple IP_3R isoforms, whereas invertebrates and some neural tissue express only IP_3R1 (434, 715, 933).

There is regional heterogeneity in the expression of IP_3R isoforms in SMCs [see (1055) for review]. Early studies identified IP_3R1 as the major isoform expressed in the vas deferens and in aortic SMCs (1095). Tasker et al. (1391), demonstrated that the other isoforms are expressed in SMCs during development, but their expression wanes as the expression of IP_3R1 increases. Proliferating SMCs express predominantly IP_3R2 and IP_3R3, suggesting specialized functions of IP_3R isoforms (1392). Rat basilar, mesenteric and thoracic arteries express predominantly IP_3R1, followed by IP_3R3 and IP_3R2 with aortas displaying lower levels of expression of all isoforms than the other vessels (498). While feed arteries and arterioles in mouse skeletal muscle express predominantly IP_3R1, in these vessels IP_3R2 was then next most highly expressed with negligible IP_3R3 (1527). Thus, IP_3R1 appears to be the most highly expressed isoform in vascular SMCs, with significant heterogeneity in the expression of IP_3R2 and IP_3R3. The functional significance of these differences is not known.

Alternative splicing of IP_3Rs

The diversity of expression of IP_3Rs is increased by alternative splicing. Three main regions of the IP_3R1 gene, all located in the long N-terminal domain, termed SI, SII, and SIII have

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been detected (306, 434); most studies have focused on the SII variants. The functional consequences of these splice variants in SMCs is not clear. In regions of the brain where only IP_3R1 is expressed, expression of the SII variant, which occurs only in IP_3R1, alters allosteric modulation of the IP_3R by phosphorylation (1343). The impact of alternative splicing on IP_3R function in SMCs where multiple IP_3Rs exist is not known (434).

Regulation of IP_3Rs by ligands

Inositol 1,4,5 trisphosphate—Inositol 1,4,5 trisphosphate is formed from hydrolysis of membrane phosphatidylinositol 1,4 bisphosphate (PIP_2) by membrane associated phospholipases whose activities are controlled by $G\alpha_{q/11}$-coupled heptihelical receptors (phospholipase Cβ; PLCβ) (Fig. 10) or tyrosine kinase receptors (PLCY) (122). Although IP_3Rs derive their name from IP_3, both IP_3 and cytosolic Ca^{2+} are required for normal activation to occur (434). IP_3 alters the sensitivity of the IP_3R for Ca^{2+}-induced inhibition: at low concentrations of IP_3, IP_3Rs are more sensitive to inhibition by Ca^{2+}, while higher concentrations of IP_3 decrease the sensitivity for inhibition by Ca^{2+} (651, 935). As noted earlier, IP_3 binds to the IBC to modulate channel gating in a Ca^{2+}-dependent fashion (330, 1280, 1282, 1395).

Calcium—Calcium ions also are important regulators of IP_3R function (Fig. 10). In the absence of IP_3, Ca^{2+} is not capable of gating the channel open (434). In the presence of IP_3, Ca^{2+} displays a bell-shaped concentration-response relationship (1434) (Fig. 10). At least eight putative Ca^{2+} binding sites have been identified, with sites located both in the SD/IBC domains, the regulatory domain, a luminal loop between transmembrane spanning domains, and within the C-terminal domain (1284). However, because the complete structure of IP_3Rs has not been resolved, the exact number and precise location of Ca^{2+} binding sites involved in gating the channels are not clear (435). It also has been shown that at nanomolar concentrations of Ca^{2+}, IP_3 binding is increased via stabilization of the IBC (1394). The inhibitory Ca^{2+} binding site may be located either on the receptor itself, or on an accessory protein (330). Low-affinity Ca^{2+}-binding sites may account for Ca^{2+}-dependent inhibition, but the location of such sites remains unclear (330).

Calmodulin—Calmodulin has been reported to bind to and modulate the function of IP_3Rs, although the significance of this interaction to the function of IP_3Rs, *in vivo* remains to be established (435). Putative calmodulin binding sites are located both in the SD and the regulatory domains of IP_3Rs (1284). As with RyRs, it has been proposed that Ca^{2+} binding to calmodulin causes a conformational change that alters its interaction with IP_3Rs and decreases channel activity (1220) (Fig. 10). However, calmodulin does not bind to IP_3R3, which still displays Ca^{2+}-dependent inhibition (435). This observation suggests that calmodulin is not required for Ca^{2+}-dependent inhibition. The function of calmodulin on IP_3Rs, *in vivo*, is still unknown. Binding studies have been conducted *in vitro*, and concrete evidence of complex formation such as coimmunoprecipitation of calmodulin and IP_3Rs have not been reported (434, 435).

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In addition to calmodulin, the Ca^{2+}-binding protein 1 (CaBP1) or related proteins such as Calmylin, in the presence of Ca^{2+} interacts with the SD and β-domains of the IBC and may stabilize interactions with adjacent monomers inhibiting channel opening (1395).

Adenosine triphosphate—Adenosine triphosphate also modulates the activity of IP_3Rs (434, 435, 933, 1485). Putative binding sites for ATP are located in the regulatory domain of IP_3Rs (434, 1284). For IP_3R1 and IP_3R3, ATP increases the sensitivity of the channels to activation by Ca^{2+} without affecting the maximal channel open probability (434, 1485). In contrast, ATP modulates the maximal open probability induced by Ca^{2+} of IP_3R2, without affecting the channel's Ca^{2+} sensitivity (434, 1485). This difference in ATP reactivity of the isoforms may allow local ATP concentrations, due to alterations in consumption or production of ATP, to differentially modulate the function of the different isoforms. However, the impact of local ATP concentrations on the function of IP_3Rs in vascular SMCs has not been established.

Protein-binding partners—Many proteins interact with IP_3Rs and potentially alter their activity (434). IRBIT (IP_3-binding protein released with IP_3) is a protein that, when phosphorylated, interacts with residues in the SD domain and IBC at the N-terminus of IP_3Rs (50, 434). Binding of IRBIT to the receptor reduces IP_3R activity, whereas IRBIT knockdown increases IP_3R activity (49). It has been proposed that this peptide functions in the negative feedback regulation of IP_3Rs.

In addition to its effects on RyRs, FKBP12 may modulate the activity of IP_3Rs (434). In colonic SMCs, FKBP12 associates with IP_3Rs and modulates IP_3-dependent Ca^{2+} release through its effects on the kinase, mTOR, and the phosphatase, calcineurin (923). IP_3Rs are also modulated by FKBP12 in portal vein SMCs (925). However, in aortic SMCs, although FKBP12 is expressed, it is not bound to IP_3Rs and does not modulate IP_3-dependent Ca^{2+} release (923). These data suggest that there are regional differences in the role played by FKBP12 in the modulation of IP_3Rs in vascular SMCs. It has also been proposed that FKBP12 alters the interaction between PKC and IP_3Rs to augment Ca^{2+} release (1143). This mechanism, however, has not been demonstrated in vascular SMCs.

Scaffolding proteins also interact with IP_3Rs. RACK1, a scaffold protein linking PKC to its substrates, also interacts with IP_3Rs within the SD and the IBC domains at the N-terminus (434, 1144). Binding of RACK1 to IP_3R increases IP_3 sensitivity and activity (1144). Ankyrin, an adaptor protein linked to the cytoskeleton, binds IP_3Rs near the pore sequence and inhibits IP_3R activity (572). Ankyrin also appears to be important for localization of IP_3Rs (434). Subcellular localization may also be mediated by interaction of IP_3Rs with the Homer family of scaffolding proteins (434). Homer binds in the SD domain at the N-terminus (434, 1435), and it has been shown that disruption of Homer cross-links to TRPC1 channels alters the activity of both channels (1611).

IP_3Rs interact with and affect the function of a number of TRPC channels including TRPC1 (163), TRPC3 (163, 756), TRPC4 (997), TRPC6 (163) and TRPC7 (1468), either directly (163) or as part of larger protein complexes (1611). Coupling sequences for interactions between IP_3Rs and TRPCs are located in the regulatory domain of IP_3Rs (434). In addition

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to TRPC channels, TRPP1 channels, when expressed in the ER, also interact with and enhance the function of IP_3Rs (5, 788, 863, 1247). This involves an interaction of negatively charged amino acids in the C-terminus of TRPP1 and positively charged residues in the SD of IP_3R (1247).

IP_3Rs also have been shown to interact with proteins involved in protecting cells from apoptosis. The Bcl family members Bcl-x_L, Mcl, and Bcl-2 bind to the C-terminus of IP_3Rs and enhance channel activity contributing to their antiapoptotic actions (368, 862).

Pharmacology of IP_3Rs

The pharmacology of IP_3Rs is outlined in Table 3. As with RyRs, the toolkit is limited, particularly because the standard method for assessing IP_3R function (Ca^{2+} imaging on whole cells) does not have the precision offered by patch clamp approaches applied to channels in the plasma membrane. There are also significant limitations with two of the agents listed; heparin and adenophostine A are not cell permeant, they must be injected into cells or dialyzed through a patch pipette. The selectivity of 2-aminoethoxydiphenyl borate (2-APB) has been questioned because it also blocks some TRP channels (156). However, in vascular SMCs this compound appears to effectively block IP_3Rs and it is the block of IP_3Rs that modulates TRPC3 channel function (1555). Nonetheless, prudent use of these compounds requires comparison of the effects of multiple inhibitors with different structures and mechanisms of action.

IP_3R function in vascular SMCs

Early studies demonstrated that inhibition of PLC attenuated myogenic tone of cerebral arteries (1114), suggesting a role for IP_3 and IP_3Rs in this process. More recent studies in the same vessels suggest a central role for IP_3Rs in generation and maintenance of myogenic tone (461, 486, 488), with Ca^{2+} release through IP_3R-activating TRPM4 channels, contributing to pressure-induced depolarization of the SMCs and subsequent activation of VGCCs. Integrin-mediated activation of PLCγ_1 and subsequent formation of IP_3 have been proposed to be the link between distending pressure and activation of IP_3Rs in this system (1036). An alternative mechanism involving pressure-induced activation of angiotensin II receptors and subsequent activation of PLCβ also has been proposed to account for IP_3 formation in renal and mesenteric arteries and could account for IP_3R activation in the myogenic response (985, 1261). Membrane depolarization, *per se*, also has been suggested to activate some G-protein-coupled receptors leading to activation of PLC, IP_3 formation, and IP_3R-dependent Ca^{2+} release (327, 419, 459, 895, 930, 1448, 1574). Thus, there may be multiple mechanisms by which intravascular pressure can lead to IP_3R signaling in vascular SMCs.

In addition to cerebral vessels, myogenic tone in skeletal muscle feed arteries and arterioles in hamsters (1528) and mice (967, 1527) also appears dependent on IP_3R signaling. In contrast, studies in fourth-order murine mesenteric arteries found no role for IP_3 and IP_3Rs in myogenic tone (966). Instead, they propose that PLC hydrolyzes phosphatidylcholine to produce DAG that is essential for myogenic tone in this murine resistance artery (966).

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Role of IP_3Rs in Ca^{2+} waves and Ca^{2+} oscillations—Regenerative release of Ca^{2+} through IP_3Rs can produce Ca^{2+} waves that propagate along cells and which can result in oscillations in intracellular Ca^{2+} (123, 434). It is thought that IP_3 primes IP_3Rs for activation by Ca^{2+}, which then, via CICR, recruits Ca^{2+} release from adjacent IP_3Rs allowing the signal to propagate along a cell (123, 434). The elevated Ca^{2+} then terminates release by Ca^{2+}-induced inhibition of the IP_3Rs, with released Ca^{2+} being transported back into the ER via SERCA (123, 434). If IP_3 levels remain elevated, this cycle can repeat resulting in oscillations in intracellular Ca^{2+} (123, 434). Calcium-dependent inhibition of PLC may lead to oscillations in IP_3, contributing to Ca^{2+} oscillations (556). The DAG produced along with IP_3 may activate PKC which, in turn, can inhibit PLC and IP_3 formation and also contribute to Ca^{2+} oscillations (537).

Role of Ca^{2+} waves in myogenic tone—Ca^{2+} waves have been reported in many types of vascular SMCs, but their role in the modulation of myogenic tone is uncertain (316). Pressurization of rat cerebral arteries leads to development of myogenic tone and an increase in the frequency of SMC Ca^{2+} waves (678, 1035, 1036). In this system Ca^{2+} waves involve both IP_3Rs (1036) and RyRs (678, 1035, 1036), and these Ca^{2+} signals appear to contribute to development of myogenic tone independent from VGCCs (1035, 1036). Pressure-induced Ca^{2+} waves that contribute to myogenic tone and which are dependent on both IP_3Rs and RyRs also have been observed in hamster and mouse cremaster muscle feed arteries (1527, 1528) (Fig. 4). However, in second-order arterioles, downstream from these feed arteries, Ca^{2+} waves also are observed, but are dependent only on the activity of IP_3Rs. In both cremaster feed arteries and arterioles Ca^{2+} waves appeared to contribute to myogenic tone, in that global intracellular Ca^{2+} fell and the vessels dilated when PLC or IP_3Rs were inhibited (1527, 1528). In cremaster arterioles, IP_3R-mediated Ca^{2+} waves appeared to be dependent on Ca^{2+} influx through VGCCs, and it was proposed that IP_3Rs amplified Ca^{2+} signals produced by Ca^{2+} influx through VGCCs (1527, 1528) (Fig. 4).

In contrast to the findings outlined in the preceding paragraph, studies in both rat (1007) and mouse (1615) mesenteric resistance arteries revealed a decrease in asynchronous Ca^{2+} waves as pressure-induced myogenic tone increased, presumably because Ca^{2+} influx through VGCCs led to inactivation of IP_3Rs. In murine mesenteric resistance arteries it was also shown that block of IP_3Rs with xestospongin C had no effect on myogenic tone (966). Thus, in these vessels IP_3Rs do appear to contribute to myogenic tone.

Studies of mouse cremaster arterioles, *in vivo*, also failed to observe Ca^{2+} waves (967), however, the sampling rate used by these authors (2 Hz) may have limited their ability to detect higher frequency events. Despite the lack of detected Ca^{2+} waves, inhibition of PLC or block of IP_3Rs dilated mouse cremaster arterioles, *in vivo* (967), consistent with *in vitro* studies of cremaster arterioles from hamsters (1528) and mice (1527). Thus, there may be regional heterogeneity in the role played by IP_3Rs in the development and maintenance of myogenic tone.

Vasoconstrictors and IP_3Rs—Many vasoconstrictors act on vascular SMCs through heptihelical receptors coupled to heterotrimeric $G_{q/11}$ and downstream PLC resulting in hydrolysis of membrane phospholipids, formation of DAG and IP_3, activation of IP_3Rs and

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subsequent release of Ca^{2+} that contributes to SMC contraction (1055, 1502) (Fig. 10). Early studies in cultured SMCs found that agonists such as thrombin (1076), vasopressin (142), ATP (931) or norepinephrine (149) stimulated oscillatory Ca^{2+} waves. Subsequent studies imaging intracellular Ca^{2+} in SMCs in the wall of resistance arteries or arterioles showed that agonists such as norepinephrine (339, 640, 734, 1150, 1602), phenylephrine (835, 965, 1007, 1059, 1224, 1288, 1530), UTP (681, 1634), U46619 (1288) or endothelin (1288) induced Ca^{2+} waves in the SMCs that were either asynchronous, inducing stable vasoconstriction, or synchronous, resulting in vasomotion (1288, 1530). Studies in SMCs isolated from rat portal vein (149), isolated rat inferior vena cava (835), rat cerebral arteries (1634) and human mesenteric arteries (1059) then provided evidence that IP_3Rs contributed to these oscillatory changes in intracellular Ca^{2+}. In several instances, RyRs also were involved in agonist-induced Ca^{2+} waves (149, 681, 1634). In rat tail arteries, downregulation of RyRs by organ culture in the presence of ryanodine eliminated RyR function, but had no effect on norepinephrine-induced Ca^{2+} waves (339). These data suggest that IP_3Rs alone are capable of supporting Ca^{2+} waves as has been shown for Ca^{2+} waves observed during myogenic tone in cremaster arterioles (1527, 1528). In rat cerebral arteries, it has been shown that IP_3R1 is the isoform responsible for UTP-generated Ca^{2+} waves (1634).

The DAG produced concomitantly with IP_3 after receptor activation, along with elevated Ca^{2+} activates PKC, which can also phosphorylate IP_3Rs and potentially modulate their function (132, 434). However, the consequence of such phosphorylation on IP_3R function is not clear (132, 434). Phorbol ester-induced activation of PKC was shown to phosphorylate IP_3Rs and increase IP_3-stimulated Ca^{2+} release from isolated hepatocyte nuclei (963). In contrast, activation of PKC decreased the activity of IP_3R2 (200) and IP_3R3 (200) in cell-based systems. Detailed studies of the effects of PKC activation on IP_3R properties have not been performed (132, 434). Thus, the role played by PKC in modulation of IP_3R function in vascular SMCs is not known.

IP_3Rs can also be phosphorylated by CamKII, although there is limited evidence that these modifications affect IP_3R activity, and the functional consequences are not known (132) (Fig. 10). There is also evidence that other serine/threonine kinases such as MAP kinases and Akt (protein kinase B), and tyrosine kinases such as Src, Fyn, and Lyn can phosphorylate IP_3Rs, but nothing is known of the functional consequences of such phosphorylation, particularly in SMCs (132).

In cerebral SMCs, IP_3R1 interacts with TRPC3 to regulate the activity of TRPC3 through a process that does not involve release of Ca^{2+} through the IP_3R1 channels (11, 1555, 1634) (Fig. 10). Jaggar and colleagues (11, 1555, 1634) propose that agonists, such as UTP, that bind to $G_{q/11}$-coupled receptors and activate PLCβ to produce IP_3 activate IP_3R1, which then interact with and activate TRPC3. The inward Na^+ and Ca^{2+} currents through TRPC3 channels depolarize the cells to activate VGCCs, increase intracellular Ca^{2+} and significantly contribute to the vasoconstriction produced by these agonists.

Vasodilators and IP_3Rs—The effects of vasodilators on IP_3R function, *per se*, in vascular SMCs have not been well studied. Both PKA (422) and PKG (1329) can phosphorylate IP_3Rs at identical sites in the regulatory domain and potentially modulate

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IP_3R activity (132, 330, 434) (Fig. 10). PKA is present in signaling complexes at IP_3R1 with AKAP9 and PP1 (132, 330, 434). Studies of IP_3Rs in heterologous expression systems have shown that PKA-dependent phosphorylation of IP_3R1 increases the channel's activity (132) (Fig. 10). In contrast, IP_3R3 seems resistant to modulation by PKA and PKG (132). However, the effects of PKA-dependent phosphorylation on IP_3R function under physiological conditions remain unclear (132, 330, 434). It has been shown in several systems, including airway SMCs (80), that elevated cAMP, via PKA, inhibits IP_3-dependent release of Ca^{2+} through IP_3Rs (4, 1400, 1614). Thus, it is possible that vasodilators that act through the cAMP-PKA signaling cascade, could act, in part, by inhibition of IP_3R function in vascular SMCs. Increased cAMP-PKA activity also can inhibit the production of IP_3 via inhibition of PLCs (4, 1051). This would indirectly inhibit Ca^{2+} release through IP_3Rs.

The cGMP-PKG signaling pathway has also been shown to inhibit IP_3-dependent Ca^{2+} release through IP_3Rs (4, 1042, 1399, 1400) (Fig. 10). However, this appears to result from PKG-mediated phosphorylation of the protein-binding partner, IP_3R-associated cGMP-kinase substrate (IRAG) (132). IRAG is a membrane bound protein in the ER that couples PKG1β to IP_3R1 (1264). Phosphorylation of IRAG at S696 inhibits agonist-induced release of Ca^{2+} through IP_3R1 (1264) and mediates cGMP-mediated relaxation of vascular SMCs (470) (Fig. 10). The cGMP-PKG signaling pathway also can inhibit formation of IP_3 via PLCs to inhibit Ca^{2+} release through IP_3Rs (4, 1051).

In rat cerebral SMCs, IP_3R1 has been shown to interact with plasmalemmal BK_{Ca} channels, and that activation of the IP_3Rs with IP_3 or adenophostin A activates the BK_{Ca} channels, providing another negative feedback mechanism to regulate myogenic tone in resistance arteries and arterioles (1635) (Fig. 10). IP_3R-related modulation of BK_{Ca} channels also has been proposed to contribute to the negative feedback regulation of tone in porcine coronary arteries (1582).

IP_3Rs and pathophysiology

Hypertension—Studies of the effects of hypertension on vascular SMC IP_3R function are limited. There is increased basal and phenylephrine-stimulated IP_3 formation in vascular SMCs from SHR (1548), and IP_3 binding capacity is increased in microsomes from vascular SMCs in the SHR (121). These data suggest that there may be increased IP_3R signaling in hypertension. However, this hypothesis has not been directly tested.

Activation of ionotropic P2X purinergic receptors has been shown to stimulate Ca^{2+} release through IP_3Rs by a mechanism that involves activation of Ca^{2+} entry through VGCCs and stimulation of PLC (1173, 1351, 1352). In renal preglomerular vascular SMCs, P2X receptor-induced IP_3R-mediated Ca^{2+} release is decreased in cells from SHR due to a decrease in the Ca^{2+} load in the SR (495). This may account, in part, for the loss of preglomerular P2X receptor-mediated reactivity that is observed in hypertension.

In contrast, in mesenteric artery SMCs, hypertension is associated with an increase in IP_3R1 protein expression and increased IP_3R function that contributes to enhanced reactivity to norepinephrine observed in hypertension (6). The increased expression of IP_3Rs appears to result from Ca^{2+}-dependent activation of calcineurin-NFAT signaling (6).

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Aging—As noted earlier in the Protein-Binding Partners section, IP_3Rs interact with, and their function is modulated by, TRPP1 channels expressed in the ER (5, 788, 863, 1247). In the cerebral circulation advanced age is not associated with a change in TRPP1 protein expression, but a decrease in the function of IP_3Rs and an apparent decrease in the modulation of IP_3Rs by TRPP1 (5). The cause of the differences observed was not established.

Diabetes—The effects of diabetes on vascular SMC IP_3R function are not clear. In streptozotocin-induced diabetes, renal glomerular, and preglomerular vascular expression of IP_3R mRNA and protein are reduced (978, 1287). Consistent with the reduced IP_3R expression, agonist stimulated Ca^{2+} signals in whole cells and IP_3-induced Ca^{2+} release in permeabilized cells also were reduced (978). These effects appeared to be mediated through transforming growth factor-β. Decreased expression and function of IP_3Rs have also been reported in aortic (918, 1274) and femoral (1274) SMCs from diabetic rats, and in A7R5 cells exposed to elevated glucose (1274).

In contrast, expression of antiapoptotic protein, Bcl-x_L, is increased in *db/db* diabetic mice resulting in augmented mesenteric vascular SMC IP_3R Ca^{2+} signaling (1471). However, the increased IP_3R-mediated Ca^{2+} signals do not appear to be the cause of the increased vasoconstrictor reactivity observed in this model of type 2 diabetes, because pharmacological inhibition of Bcl-x_L effects reduced Ca^{2+} signals, but had no effect on contractility (1471).

Transient Receptor Potential Channels

Discovery of TRP channels

Transient receptor potential (TRP) channels were first discovered and characterized in *Drosophila melanogaster*, after a mutation to Chromosome 3 resulted in offspring that were visually impaired in normal light but showed normal phototaxis under low light (277). Further experiments uncovered that the normal, prolonged increase in photoreceptor membrane potential associated with light exposure was absent; instead, exposure to light resulted in a transient increase in voltage that rapidly decayed back to baseline. This characteristic phenotype lead to these mutants being named “transient receptor potential,” or *trp*, mutants (277, 1006). It was postulated later that the protein product of the *trp* locus was probably a cation-permeable ion channel, since hydrophobicity plots predicted a 6 to 8 transmembrane domain structure similar to that of known voltage-dependent ion channels (1023). However, the “*trp* channel” lacked the positively-charged amino acid sequence in the S4 region that normally imparts voltage sensitivity, suggesting the channel did not respond to depolarization (1158). Instead, the *trp* channel was found to be a Ca^{2+}-permeable nonselective cation channel, which was activated by the SERCA inhibitor thapsigargin and opened subsequent to IP_3-mediated Ca^{2+} release from intracellular ER Ca^{2+} stores (1023, 1450). Expression of “TRP” and “TRP-like” proteins was subsequently discovered in most eukaryotic species, where the channels are key mediators of cation flux in both excitable and nonexcitable cells (260, 1086).

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Structure and general function of TRP channels

In mammals, 28 TRP channels have been identified and grouped by sequence homology into 6 distinct families: canonical (TRPC1–7), melanostatin (TRPM1–8), vanilloid (TRPV1–6), ankyrin (TRPA1), polycystin (TRPP1–3), and mucolipin (TRPML1–3) (1121). Individual TRP channels are tetramers, with each subunit containing six transmembrane domains and intracellular C- and N-termini of varying amino acid length. These termini contain multiple protein binding sites, enzymatic domains, and regulatory elements that also differ between families and channel subtypes (258). TRP channels can exist as both homo- and heteromultimers, which further increases the diversity of their function and activity (258, 259, 333, 361, 658, 1347). With regard to the function of TRP channels in vascular SMCs, members of each family (with the exception of TRPML) have been implicated in regulating SMC contractility in different vascular beds (361).

The general properties of each TRP channel family, common familial characteristics, and relevant differences in channel structure are described in this section. Their individual contributions to vascular tone are discussed in subsequent sections.

Canonical (TRPC) channels—The seven members of the TRPC family were named “canonical” [or “classical” (260)] due to their close structural resemblance and sequence homology to the original *trp* channel discovered in *D. Melanogaster* (1525, 1648, 1655). With the exception of TRPC2 (a pseudogene in humans and rats), the remaining TRPC channels can be subdivided into two groups by sequence homology: TRPC1/C4/C5 and TRPC3/C6/C7 (875, 1553, 1601). The general structure of TRPC channels is relatively similar. Each subunit contains the requisite six transmembrane domains, 3–4 ankyrin repeats and a coiled-coil domain on the N-terminus, and a C-terminus containing a calmodulin/IP_3R binding (CIRB) domain and the “TRP box” sequence (EWKFAR) common to all TRP channels (258, 1101, 1469, 1553). Additionally, TRPC4 and TRPC5 contain a common structural domain originally found in Postsynaptic density protein 95, Drosophila disk large tumor suppressor protein and Zona occludens 1 (PDZ-binding motif) on their C-termini that is crucial for protein/protein interactions between these channels and several signaling molecules (46, 757, 1387). The PDZ motif, and an additional coiled-coil domain, may also lead to the extensive heteromultimerization that exists between TRPC1, TRPC4 and TRPC5 (880, 1346, 1347). TRPC3/C6/C7, however, largely exist as homomultimers (1553). TRPC channels show little ion selectivity, favoring Ca^{2+} conductance over Na^+ with a ratio of 1:1 to 5:1 (1258, 1347, 1469, 1654).

Members of the TRPC family are part of receptor-operated Ca^{2+} entry (ROCE) pathways, since they are activated downstream of $G_{q/11}$-coupled receptors and receptor tyrosine kinases that activate phospholipase C (1166, 1167, 1387, 1426, 1553). A detailed description of G protein-coupled receptors that activate TRPC channels is presented in (8). Several canonical family members are also activated by DAG, through a mechanism that is independent of traditional PKC-mediated channel phosphorylation (562, 612, 836, 880, 1536). This finding further reinforces the direct relationship between TRPC channels and the activation of membrane-bound receptors. Given their downstream association with PLC activation and the presence of a CIRB-binding site, it has been long-proposed that TRPC channels open in

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response depletion of intracellular Ca^{2+} stores, and thus would be the dominant source of store-operated Ca^{2+} entry (SOCE) as well (47, 669, 756, 1240, 1263, 1525). However, TRPC channels lack the typical store-operated gating mechanisms present in other SOCE channel complexes (e.g., STIM1/Orai) (51, 328, 858). Simultaneous knockout of TRPC1/4/5 channels resulted in no change to neuronal SOCE, indicating that activation of TRPC channels is indeed not required (564). Furthermore, the lack of Ca^{2+} selectivity inherent to the TRPC channels (601) and the absence of SOCE in many types of contractile SMCs (1170, 1425, 1555) have largely eliminated TRPC channels as SOCE channels in vascular smooth muscle. Thus, TRPC channels are most appropriately described as receptor-operated cation channels.

Melastatin (TRPM) channels—With its 8 members, the TRPM channels are the largest subfamily of TRP channels (431). TRPM channels received their name because the first identified member, TRPM1, was discovered while screening for genes downregulated in mouse melanoma tumor-cell lines (350, 1565). Structurally, all TRPM channels contain the typical C-terminal TRP-box sequence and an N-terminal coiled-coil region that is also common to most TRP channels (386, 448, 503, 1022, 1091, 1156). However, TRPM channels lack the N-terminal ankyrin repeats present in TRPC, TRPA, and TRPV channels (561). Instead, an additional ~700 amino acid TRPM homology domain on the N-terminus is conserved in all 8 TRPM family members (431). As with the TRPC channel family, TRPM channels can be further subdivided into four pairs, based on mechanisms of activation, structural homology, and biophysical properties: TRPM1/M3, TRPM2/M8, TRPM4/M5, and TRPM6/M7 (1553).

TRPM1 and TRPM3 channels are both constitutively active and nonselective for Ca^{2+} *versus* Na^{+} (431, 503). The activity of TRPM3 can also be augmented by hypotonic solutions, suggesting a role in osmolarity sensation and Ca^{2+} homeostasis in the kidney (503, 563). While TRPM2/M8 are the closest-related family members (42% sequence homology and relatively little cationic selectivity (980, 1146, 1155)), their activation and regulation are entirely different from one another. TRPM2 channels are activated by oxidative and nitrositive stress, due to in part to a C-terminal Nudix-like domain that hydrolyzes ADP ribose and leads to channel opening (790, 1155, 1156). This domain is absent in TRPM8. Instead, the C-terminus of the TRPM8 channel contains a PIP_2 binding domain and structural elements involved in temperature-dependent gating, which imparts TRPM8's well-characterized cold/menthol-sensitivity and PIP_2-dependent activation (172, 1213).

TRPM4/5 are the only two members of the TRPM family that show marked selectivity for Na^{+} over Ca^{2+} (Ca^{2+}/Na^{+} = <0.05), and are virtually impermeable to all other divalent cations (610, 824). TRPM4/M5 are activated by increases in intracellular Ca^{2+} concentration, and are thus purported to function primarily as a Ca^{2+}-activated, monovalent cation-conducting channel (610, 1085, 1087, 1091). Structurally, TRPM4 and TRPM5 both contain voltage-sensing domains (originally thought to be absent from TRP channels), PIP_2/calmodulin binding sites, and phosphorylation sites that regulate the Ca^{2+} sensitivity and voltage dependence of channel opening (431, 1088, 1091).

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The ubiquitously-expressed TRPM6/M7 channels are fusion proteins, comprised of the traditional ion channel transmembrane domains coupled to an enzymatically active α-kinase domain (252, 430). While selective for divalent cations over monovalent cations, TRPM6/M7 have a fivefold greater selectivity for Mg^{2+} over Ca^{2+} and thus are key to Mg^{2+} homeostasis (1633). Both channels are also activated by acidic pH (853). The endogenous substrate(s) for TRPM6/M7 α-kinase activity are unclear, although *in vitro* studies suggest that both TRPM6 and TRPM7's α-kinases can phosphorylate myosin IA, IIB, and IIC on identical residues (261). Furthermore, the TRPM6 and TRPM7 channels coassemble into heteromultimers, leading to regulation by both auto- and cross-phosphorylation by their respective kinase domains (253, 261, 1266, 1633).

Vanilloid (TRPV) channels—The six members of the TRPV family are so named because of their activation by vanilloid-like compounds (e.g., capsaicin) (206, 1415). While vanilloid-dependent activation is a common trait of TRPV channels, they are critical for the regulation of nociception, thermosensation, mechanosensation, and Ca^{2+} absorption/reabsorption (112, 1415, 1473). TRPV channels can be broadly subdivided into two groups, based on their Ca^{2+} selectivity: TRPV1–V4 (P_{Ca}/P_{Na} = ~1–10) and TRPV5/V6 (P_{Ca}/P_{Na}>100) (258, 259, 1473, 1474). Similar to the TRPC family, heteromultimerization between channels within each group has been reported (585, 787, 873). All TRPV channels contain 3–5 N-terminal ankyrin repeats, as well as the conserved TRP-box sequence (1474). Specific residues in the transmembrane domain linkers of TRPV1–V4 impart thermal and proton sensitivity, and TRPV1, V4, V5, and V6 also contain C-terminal CaM-binding sites (134, 413, 462, 777, 1594). TRPV5/V6 are weakly voltage-sensitive, and are the only TRP channels that are almost completely selective for Ca^{2+} (1473).

Ankyrin (TRPA) channels—A sole member of the TRPA family, TRPA1, is expressed in mammalian cells (1659). This family is named "ankyrin" due to the 14 to 18 ankyrin repeats on the N-terminus of the channel, which makes up over half the total size of the TRPA1 monomeric protein (466, 1090). The TRPA1 channel is nonselective for monovalent or divalent cations (P_{Ca}/P_{Na} = 0.84) (1046), but is bi-modally regulated by intracellular [Ca^{2+}]—much like the IP_3 receptor (*discussed earlier*). Low concentrations of intracellular Ca^{2+} potentiate TRPA1 activation, whereas high concentrations inhibit channel opening (1491). The physiological roles of TRPA1 channels include nociception, cold temperature sensation, and chemosensation (324, 732, 1090, 1340, 1492). Pungent chemicals, such as mustard oil [allyl isothiocyanate (AITC)] and cinnamaldehyde, reversibly activate TRPA1 through covalent modifications of N-terminal cysteine residues (603). The massive relative size of the N-terminal tail begat the hypothesis that TRPA1 may also be a mechanosensitive channel (626), but this has yet to be confirmed *in vivo* (324, 1340).

Polycystin (TRPP) channels—The TRPP family originally included two subsets of proteins, both of which are related to the development of polycystic kidney disease (PKD): PKD1 and PKD2 (1278). Members of the PKD1 group turned out to have 11 transmembrane domains that did not form functional ion channels (609). Members of the PKD2 group, however, are 6-TM domain proteins that assemble to form an ion-permeable pore, and are generally now regarded as sole members of the "TRPP" family of TRP channels (259, 609,

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1278). This early confusion has led to relatively confusing nomenclature surrounding the TRPP channel family, from a historical perspective. To alleviate such confusion, and based on the nomenclature given in the 2016 International Union of Basic and Clinical Pharmacology (IUPHAR) Database (259), “TRPP1,” “TRPP2,” and “TRPP3” in this review will refer to “PKD2,” “PKDL1,” and “PKDL2,” respectively, as found in earlier literature. While evidence suggests PKD1 proteins do associate with TRPP channels in macromolecular signaling complexes (1278), their role and function will not be discussed in this review. See several outstanding reviews on this subject for more information (609, 1278, 1553).

The TRPP channels share a similar topology to the other TRP channels, with the exception of a large extracellular loop between the S1 and S2 transmembrane helices (609, 1019, 1278). TRPP1–P3 channels are relatively nonselective for Ca^{2+} ($P_{Ca}/P_{Na} = 6$) (258, 1086). Little is known about the physiological significance for TRPP channels other than their roles in left/right symmetry development and in the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD) (609). Activation of TRPP1 is vaguely understood, and is further complicated by the fact that TRPP1 channels locate in multiple subcellular compartments, including the endoplasmic reticular membrane, the plasma membrane and primary cilia (433, 788, 1145). TRPP2 channels are implicated in sour taste sensation as they are activated by intracellular Ca^{2+} and inhibited by low extracellular pH (658). Recent evidence also suggests that TRPP2 channels are weakly voltage-dependent and sensitive to cell swelling (1297, 1298). No spontaneous activity has been observed when the TRPP3 channel is overexpressed, and thus no relevant function is yet clear (1362).

Expression and function of TRP channels in vascular SMCs

Of the TRP channel subfamilies described earlier, at least 12 have been detected in SMCs across most vascular beds. In this section, the important functions of the vascular TRP channels will be covered for each family, in terms of the physiological stimuli to which they respond: endogenous messengers (e.g., DAG, intracellular Ca^{2+}, and GPCR activation); activation by exogenous stimuli (e.g., temperature, noxious chemicals, and osmotic stress); and mechanical stresses (e.g., pressure-induced tone). In some cases, the functions of TRP channels in the vasculature have relied heavily on the use of nonselective pharmacological agents (*see Section “Pharmacology”*). As such, prudence should be used when interpreting these data with regard to the role of TRP channels in SMC contractility. Also, for more information regarding TRP channel distribution in different vascular beds, see Earley and Brayden (361).

TRPC channels: Receptor-operated Ca^{2+} entry and membrane depolarization

—As stated above, TRPC channels have long been implicated in ROCE and SOCE, especially in vascular SMCs (30, 846, 1166). The complex heteromultimerization of the TRPC channels, and differences in subtype expression and association throughout the vasculature, led to significant difficulty in isolating the exact contributions of each TRPC channel subtype to these two Ca^{2+} entry processes. To date, evidence supports an important role for 5 members of the TRPC family in smooth muscle: TRPC1, TRPC3, TRPC4,

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TRPC5, and TRPC6. Their individual and collective contributions to vascular tone are described below.

TRPC1 was originally linked to ROCE and SOCE in and of itself (118, 645). Endothelin-1 caused ROCE in cerebral arteries and cultured aortic SMCs in a TRPC1-dependent manner (1372), and in pulmonary artery SMCs, activation of SOCE (by blocking SERCA) was mediated by STIM1 and subsequent Ca^{2+} entry through TRPC1 channels (1078). However, this was refuted in later studies using TRPC1 knockout mice, which showed no differences in SOCE in aortas and cerebral arteries (334). Phenylephrine-induced constriction was also augmented in TRPC1 knockout mice and was unchanged in TRPC3 knockout animals, suggesting that TRPC1 channels are involved in ROCE instead (772). The role of TRPC1 in vascular contractility is further complicated by the finding that TRPC1 forms heteromultimers with TRPC5 (1293, 1294). It has also been proposed that TRPC1 channels are part of a larger signaling complex with non-TRP ion channels in vascular SMCs. In aorta and mesenteric arteries, TRPC1 immunoprecipitated with BK_{Ca} channels, and that Ca^{2+} influx through TRPC1 activated BK_{Ca} channels to hyperpolarize the SMC membrane and oppose vasoconstriction (806). Another model proposed an association between TRPC1, STIM1, and IP_3 receptors that accounted for SMC contraction (150, 361, 1620). TRPC1 may be involved in ROCE only, regulating GPCR-mediated vascular contractility through interactions with BK_{Ca} channels or TRPC5 channels.

As with TRPC1, TRPC3 is implicated in vasoconstriction in response to several endogenous ligands for GPCRs. Responses to UTP in cerebral arteries, ET-1 in coronary arteries, and angiotensin-II in aorta, all involve activation of TRPC3 (894, 1151, 1194). TRPC3 is also capable of forming heteromultimers with TRPC1 and TRPC6, and this complex participates in norepinephrine-induced constriction of afferent arterioles (1243). Downregulation of TRPC3 channels also had no effect on pressure-induced (“myogenic”) tone development in pial arteries (1194), suggesting the role for TRPC3 was limited to GPCR-mediated responses—perhaps through direct activation of the channel by DAG, as had been previously suggested (32, 821, 1459). However, several reports associated opening of TRPC3 channels with activation of IP_3 receptors on the sarcoplasmic reticulum. IP_3 constricts cerebral arteries via IP_3R-mediated activation of TRPC3 (1555). Additionally, ET-1 causes vasoconstriction via direct interaction of IP_3R1 and TRPC3 (12). TRPC3 and IP_3R1 associate with caveolin-1 in a macromolecular complex which, when disrupted, interferes with IP_3-induced activation of TRPC3 channels (11). Lastly, TRPC3 function can be mediated by direct action of several different kinases, although this regulation may be tissue specific (361). WNK4 and PKG inhibit TRPC3 function in rat aorta and carotid artery, respectively (226, 1131). However, studies with TRPC3 knockout mice failed to confirm this relationship in mouse aorta or hind limb vasculature (899). Taken together, these data suggest TRPC3 function is controlled by multiple mechanisms initiated by phospholipase activation, but these pathways may involve both DAG- and IP_3R-mediated regulation of the TRPC3 channel and direct interaction between TRPC3 and IP_3Rs (*see* Fig. 11).

Even though both channels are expressed throughout the vascular tree (439, 1641), the individual roles of TRPC4 and TRPC5 in smooth muscle contractility are the least clear of the canonical TRP family members. TRPC4 channels (along with TRPC1 and TRPC5) have

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been implicated in SOCE in pulmonary arterial SMCs (859). Prolonged, cyclic stretch reduced TRPC4 expression and SOCE in rat mesenteric arteries (878). However, no direct measures of TRPC4-mediated changes in vascular SMC contractility have been reported. Changes in vascular tone have been reported after removal of TRPC4 from endothelial cells (438), but even these findings are not without controversy (361, 1301). Little information exists as to the role of TRPC5 alone; rather, TRPC5 is best described as a heteromultimer with TRPC1, TRPC6, or TRPC7 (1238).

TRPC6 channels are well described in both venous and arterial smooth muscle, where they play an important role in regulating contractile function downstream of PLC activation (see Fig. 11). Cationic currents seen subsequent to α_1-adrenoreceptor activation in portal vein myocytes were discovered to be through TRPC6 channels (647). Other GPCRs also activate TRPC6 currents: vasopressin activates TRPC6 in A7r5 cells (719), and angiotensin II also does so in mesenteric artery SMCs (33). This activation is due to direct interaction of DAG with the TRPC6 channel, and not through indirect phosphorylation by protein kinases (820, 1239). Interestingly, the precursor of DAG—PIP_2—has an inhibitory effect on TRPC6 channel function in arterial SMCs, which is not seen in other expression systems (33, 841). This suggests a coregulatory mechanism, by which PLC activation both relieves TRPC6 channel inhibition by PIP_2 and causes channel activation by DAG. Additional reports describe a synergistic relationship between activation of TRPC6 channels by both DAG and IP_3, with IP_3 alone having no effect on channel opening (31, 718).

In addition to receptor-mediated Ca^{2+} signaling, TRPC6 is also involved in the development of pressure-induced (myogenic) tone (see Fig. 11). Myogenic tone is largely regulated by pressure-dependent depolarization of SMCs, which results in the opening of VGCCs, Ca^{2+} influx, and vasoconstriction (315, 600, 993, 1073). TRPC6 channels appear to be integral in the development of myogenic tone of cerebral arteries (1523), but not mesenteric arteries (1261). However, it is not clear how mechanical forces activate the TRPC6 channel, nor is it clear the functional role that cationic influx through TRPC6 channels has in regulating myogenic tone. It is possible that, as with receptor-mediated constriction, TRPC6 channels are activated downstream of PLC activation. Activation of PLC by mechanosensitive GPCRs plays a role in myogenic tone development in small cerebral arteries (985, 1114), which would support the idea that TRPC6 serves as a parallel Ca^{2+} influx pathway to VGCCs. Others have described direct mechanical activation of TRPC6 in SMCs, independent of PLC activation (1331, 1523), but not without controversy. Calcium influx through TRPC6 channels during myogenic tone development appears to supplement or trigger IP_3R-mediated Ca^{2+} release, which subsequently activates TRPM4 channels, contributing to pressure-dependent membrane depolarization (488). Given the level of mechanistic complexity and variability across the vasculature, the importance of TRPC6 channels in regulating vascular tone remains unclear and their function in the development and regulation of myogenic tone should be further explored.

TRPM channels: SMC depolarization and myogenic tone—While the TRPM channels represent the largest family of TRP channels in quantity, only two members are expressed in vascular SMCs: TRPM4 and TRPM8 (360, 712, 1358). TRPM4 channels have been found throughout the vascular tree, and are present in myogenically active resistance

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arteries and large conduit arteries alike (360). As mentioned earlier, TRPM4 is impermeable to divalent cations; TRPM4 is instead responsible for Na^+ influx that causes membrane depolarization of SMCs (367). To that end, TRM4 channels show some degree of voltage dependence in their activation. These channels inactivate rapidly at negative membrane potentials, but have large, slow-activating currents at more positive potentials (1087). This voltage sensitivity appears to be due to an intrinsic voltage sensor and not blockade of the ion pore by divalent cations (1087). Also, Na^+ currents through TRPM4 channels exhibit time-dependent inactivation and are regulated both by PKC and intracellular Ca^{2+} concentration (360, 366, 367). The concentrations of Ca^{2+} required to activate TRPM4 channels are extremely high (10–100 μmol/L), which far exceed even the highest global intracellular Ca^{2+} concentrations in normal SMCs and suggests a local Ca^{2+} event (similar to a Ca^{2+} spark) is required. As shown in Figure 11, the local bursts of Ca^{2+} needed to activate TRPM4 channels were found to originate from IP_3 receptors in close proximity to TRPM4 channels in the plasma membrane (486, 487).

In cerebral arteries, TRPM4 channels appear to mediate myogenic tone development through a mechanism that also involves PLCγ1 activation, TRPC6, and IP_3Rs (488). Inhibition of TRPM4 with either 9-phenanthrol or siRNA, inhibited pressure-induced tone development, but not UTP-mediated constriction, suggesting that TRPM4 channels are specifically involved in regulating membrane depolarization in response to changes in intravascular pressure and not contractile agonists (367, 1194). However, knockout of TRPM4 resulted in a hypertensive phenotype and no appreciable change to either myogenic or agonist-induced vascular tone of the hind limb (958). While the hypertensive phenotype was attributed to increases in circulating catecholamines, no explanation for the lack of change in myogenic tone in the hind limb resistance vasculature was readily apparent. Thus, it remains unknown if the regulation of myogenic tone by TRPM4 is specific to the cerebral vasculature, or if parallel mechanisms exist by which myogenic tone can be controlled in other vascular beds.

To date, few studies show the presence of TRPM8 channels in vascular SMCs. In aorta, mesenteric artery, and femoral artery, TRPM8 activation results in a modest relaxation that is endothelium independent (712). Another study concluded that TRPM8 played a part in mesenteric artery vasodilation in rats, but some of the pharmacological tools used bring the specificity of this conclusion into question (1305). Thus, the role of TRPM8 channels is still relatively unknown.

TRPV channels: Responses to temperature, endocannabinoids and EETs—Of the vanilloid family, TRPV1, TRPV2, and TRPV4 channels have all been found to play a functional role in vascular SMC tone in different vascular beds (99, 427, 1419). TRPV1 channels are expressed in aortic and skeletal muscle arteriolar SMCs as well as arterioles from thermoregulatory tissues (e.g., skin and ear) (733, 897, 1034, 1419, 1467). In these tissues, activation of TRPV1 by capsaicin resulted in endothelium-independent vasoconstriction, decreased hind limb perfusion, and increased gracilis muscle vascular resistance (733, 1034, 1467). TRPV1 activation can also cause vasodilation, but this is in an endothelium-dependent manner and not attributed to SMC TRPV1 (1626).

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In isolated mesenteric artery SMCs, TRPV2 channels are activated by endocannabinoids and may result in vasodilation (99, 1181). Although not related to contraction, TRPV2 channels appear to be activated by several vascular growth factors to contribute to SMC migration (1339). However, TRPV2 channels in pulmonary artery SMCs are responsible for nonselective cation currents activated by thromboxane A2 during hypoxia (1606). Nonetheless, whole-vessel studies are still lacking, and as such the role of TRPV2 channels in vascular tone is not yet clearly defined.

A broad body of evidence links endothelial TRPV4 channels to vasodilation in mesenteric arteries and peripheral arterioles (365, 604, 1325), but TRPV4 channels are also expressed in SMCs and have a role in regulating vascular tone. In cerebral artery myocytes, TRPV4 channels temper the vasoconstrictor responses to angiotensin-II through a mechanism dependent on PKC and AKAP150 (994). There is also an important connection between SMC TRPV4 and BK_{Ca} channels, which drive SMC hyperpolarization in response to EETs (365, 427, 917, 994, 1482). These findings suggest that smooth muscle TRPV4 channels, similar to endothelial TRPV4 channels, are anchored by AKAP150 into a subcellular signaling complex. In SMCs, however, this complex includes PKC, BK_{Ca} channels and GPCRs, and regulates vasodilation.

TRPA and TRPP channels: Mechanosensitive vasodilation—The least well-characterized TRP channels in vascular smooth muscle are the TRPA1 channel and the TRPP1 channel. Unlike most of the TRP channel family members described above, both TRPA1 and TRPP1 are linked to vasodilation, either directly or indirectly. TRPA1 channels are predominantly involved in endothelium-dependent vasodilation (362, 1265, 1353), but were also shown to be involved in endothelium-independent relaxation of aortic rings by cinnamaldehyde (1579). However, this study did not confirm SMC-specific expression of TRPA1. Cerebellar arteries did express mRNA and positive immunofluorescence for TRPA1, but no endothelium-independent response to the TRPA1 agonist AITC was seen (359, 363). This suggests that TRPA1 may only play a role in large conduit arteries, or the response was due to non-specific effects of cinnamaldehyde (926). In either case, the function of TRPA1 channels in vascular SMCs remains unclear.

Originally, TRPP1 channels were assumed to aid in cytoskeletal arrangement and organization during SMC differentiation through associations with PKD1 (501, 1285). In the presence of PKD1, TRPP1 seemed to have little effect on contractility; it was only after knockout of PKD1 that myogenic tone was decreased in mesenteric arteries (1285). Interestingly, knockdown of TRPP1 in the same PKD1 knockout animals recovered normal myogenic constriction of mesenteric arteries (1285). TRPP1 knockdown also resulted in increased constriction of aortae and mesenteric arteries in response to the adrenergic agonist, phenylephrine (343, 1180). These data suggested that, when activated, TRPP1 currents opposed the development of myogenic constriction in peripheral and conduit arteries. In the cerebral arteries, however, TRPP1 knockdown had the opposite effect: myogenic tone development was decreased, and cell swelling-induced cation currents were reduced (1056). The exact role of TRPP1 in vascular SMCs will require more investigation to determine the reasons for these diametric roles in different segments of the vascular tree.

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TRP channel pharmacology

The vast overlap and interplay among TRP channels has resulted in an extremely complex and confusing pharmacopoeia. With the exception of capsaicin (TRPV1), the selectivity and specificity of the pharmacological tools used to investigate TRP channels is questionable, at best (926, 1553). Table 4 summarizes TRP channel pharmacology, in terms of activation of the channel, ionic selectivity, agonists, and antagonists. The agonists and antagonists in the table were selected by their relative specificity for each TRP channel subtype. Due to the aforementioned lack of specificity of many of these compounds at higher concentrations, drugs with defined IC_{50} and EC_{50} values were used wherever possible. Individual concentrations are not reported to avoid confusion; however, the provided references will contain such information. A more in-depth description of TRP channel pharmacology can be found in the IUPHAR/BPS Database of Receptors and Ion Channels (259).

Most agents were originally believed to exhibit subfamily specificity, but were later found to have broad actions across multiple TRP channels and channel families. This includes drugs such as SKF96365, ruthenium red, and flufenamic acid (647, 720, 979, 1046, 1148). Other agents, such as 2-APB, were found to both activate and inhibit TRP channels in a concentration- and subtype-specific manner (853, 1568). Nonetheless, the broad-spectrum TRP channel agonists and antagonists have been used with much success as part of a “process of elimination” of TRP channel currents measured from vascular SMCs. Large di- and trivalent metal cations (e.g., La^{3+}, Gd^{3+}, Ni^{2+}, and Zn^{2+}) have also been used to differentiate between different TRP channel family members (164). However, these have proven difficult to use in whole vascular tissues due to their propensity to interfere with other ion channels and the often high concentrations required for TRP channel block or activation (259). This “dirty” pharmacology highlights the need for parallel studies, using tissue-specific knockout animals or alternative inhibition techniques (e.g., siRNA and viral vectors), to properly understand and elucidate individual TRP channel functions.

TRP channels and pathophysiology

Due to the broad involvement of TRP channels in regulating mechanical- and agonist-induced responses in the vasculature, defining specific roles for individual TRP channels in disease has proven extremely difficult. Nonetheless, several TRP channels are identified as having important roles in the pathophysiology of cardiovascular diseases.

Hypertension—Considering that SMC TRP channels largely mediate cationic fluxes that are necessary for contraction, augmentation of TRP channel function should lead to increased SMC tone and reactivity. Thus, it is not surprising that many of the TRP channels expressed in vascular SMCs have been implicated in the pathogenesis of hypertension. TRPC3 channels are implicated in the pathogenesis of hypertension through differential phosphorylation by the serine threonine kinase, WNK4, which suppresses channel activation and leads to SMC hypertrophy, increased myogenic tone and hypertension (1131). Regulation of TRPC3 is also linked to vascular pathology in hypertension through mechanisms affecting endothelial cell and immune cell signaling (1404, 1405). While TRPM4 knockout animals are also hypertensive, this appears to stem from an increase in circulating catecholamines and not a change in SMC reactivity alone (958). TRPM7

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channels may also play a role in essential hypertension: SHRs show decreased TRPM7 expression and decreased intracellular Mg^{2+}, both of which are linked to the actions of angiotensin II (1420).

Unlike essential hypertension, TRP channels may be a promising target for the treatment of pulmonary arterial hypertension (PAH). Both TRPC1 and TRPC6 expression is increased in pulmonary arteries during hypoxic conditions similar to those caused by PAH (876). Additionally, TRPV4 channels are upregulated in chronic hypoxia-induced PAH in mice and rats (1558, 1585) with no change in TRPM channel expression under the same conditions (1585). However, this is in conflict with other researchers, who showed a dramatic decrease in TRPM8 expression in pulmonary arterial myocytes in animal models of PAH (889, 1586).

Aging—Generally, the roles of TRP channels in age-dependent changes to vascular tone are vastly undefined beyond a few specific examples. Knockout mice lacking TRPP channels develop age-dependent hypercontractility in large conduit vessels (567). Aged hypertensive rats also showed maladaptive changes to middle cerebral artery myogenic tone and Ca^{2+} signaling, which was associated with decreased TRP channel-mediated Ca^{2+} responses (1418). Further research is needed to determine the roles of other TRP channels in aging.

Diabetes—Vessels from diabetic patients are more reactive than nondiabetic controls (1106), a finding which may be linked to changes in SMC TRP channel function. In human saphenous vein, diabetic vessels were more reactive to cyclopiazonic acid; this response was also inhibited by the TRP channel blocker SKF-96365 (254). This change in response was associated with increased TRPC4 expression, and decreased TRPC1 and TRPC6 expression in the diabetic vessels (254). Additionally, TRPV1 channel expression and capsaicin-mediated vasodilation are decreased in coronary arteries from diabetic mice (511).

Conclusions and Remaining Questions

Decades of studies have widely advanced our knowledge of the expression of ion channels in vascular smooth muscle and their roles in regulating tone and tissue perfusion. However, a broad analysis of the current literature still leaves fundamental questions unanswered while providing new insight into the complex interplay of these channels in health and disease. We suggest several such questions that warrant further investigation.

While it is clear that L-type VGCCs composed of Ca_V 1.2 channels importantly contribute to myogenic tone and its modulation by vasoconstrictors and vasodilators, a number of questions remain concerning these channels and the expression and function of other VGCCs in resistance arteries and arterioles around the body. Why do L-type VGCCs appear silent in some *in vivo* preparations? Do Ca_V 3.2-based T-type channels contribute to the negative-feedback regulation of myogenic tone in all vascular beds? What is the role of other VGCCs?

Studies have shown a remarkable number of K_V channel isoforms expressed in vascular SMCs around the body. However, our understanding of the integrated function of the different classes of K_V channels is limited. For example, studies in rat middle cerebral

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arteries indicate that at least three classes of K_V channels (K_V 1, K_V 2, and K_V 7) are expressed and contribute to the regulation of SMC membrane potential and the negative-feedback regulation of myogenic tone [see (1643) and references therein]. In these vessels, it has been proposed that the unique voltage dependence of activation and inactivation of each of these K_V channels provides precise negative-feedback control of membrane potential across of broad range of voltages, allowing myogenic tone to be precisely regulated across a wide spectrum of blood pressures (1643). However, this remains speculation and has not been critically tested in other blood vessels, and particularly, *in vivo*.

Our understanding of the expression and function of RyR and IP_3R isoforms and their regulation in the context of vascular SMCs in resistance arteries and arterioles is very limited. Why do RyRs appear to be silent in arterioles? Why do IP_3R-dependent Ca^{2+} waves not activate BK_{Ca} channels? Do Ca^{2+} waves contribute to functions other than contributing to global Ca^{2+} signals in the regulation of resistance artery and arteriolar SMC function?

While evidence continues to mount as to the importance of TRP channels in the development of vascular tone, our understanding of the mechanisms by which TRP channels are regulated in vascular SMCs has only just begun. TRP channels represent the most logical means to transduce changes in the physical environment into changes into vascular function, but the paucity of selective pharmacological agents has limited our ability to explore these possibilities. Future questions include: how does the proximity of TRP channels to one another affect vascular tone? What endogenous ligands activate and/or inhibit TRP channel function? How can we differentiate the functions of homomeric from heteromeric TRP channels, and do these arrangements change in disease? How can we design better drugs to target these channels with some degree of specificity? Even with these questions unanswered, the evidence that TRP channels are integral in regulation of myogenic and agonist-induced tone is without contestation.

Disease states often lead to altered SMC ion channel expression and/or function. However, it is not often clear whether the changes that occur are part of the disease progression, or a compensatory change in an attempt to maintain homeostasis. It is suspected that the use of different disease models with different time courses of progression, severity and root cause, while important to try and understand the spectrum of human and animal disease, has left a confusing picture of the contribution of altered SMC ion channel expression and function to a given disease. Additional research identifying the signaling pathways responsible for altered SMC ion channel function and expression, the time course and the dose-response relationships between disease severity and ion channel dysfunction are needed to resolve these issues.

We have focused on SMC ion channels in this review. However, we fully acknowledge that in intact resistance arteries and arterioles, SMCs are electrically coupled to underlying endothelial cells by myoendothelial gap junctions, and that endothelial cells also express their own cadre of ion channels (671). While it is known that hyperpolarization of endothelial cells (induced by opening of K_{Ca} channels in these cells) can be transmitted to overlying SMCs (i.e., via EDHF), the impact of other endothelial cell ion channels on the regulation of membrane potential and function in the overlying SMC remains largely

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speculative, because the tools currently available to electrically uncouple these cell layers (mechanical denudation, available gap junction inhibitors, etc.) are simply too blunt.

Ion channels in the plasma membrane and in the ER of SMCs importantly contribute to the generation and maintenance of myogenic tone, as well as the mechanism of action of vasodilators and vasoconstrictors in resistance arteries and arterioles. Diseases such as hypertension, obesity, the metabolic syndrome, and diabetes alter the expression and function of SMC ion channels, contributing to vascular dysfunction and pathogenesis. While much has been learned about the structure, biophysics and function of the myriad of channels expressed in vascular SMCs, significant gaps remain in our understanding. Regional and species heterogeneity have made the study of ion channel function in vascular SMCs difficult because investigators cannot extrapolate between regions and systems, except in the broadest terms. Also, because we now know that ion channels exist in large macromolecular complexes, our understanding of the entire repertoire of regulatory mechanisms is hindered by lack of knowledge of all proteins with which a given channel interacts within the context of the vascular bed and physiological (or pathophysiological) status of the blood vessel in question. Trying to understand the function of an ion channel in a vascular SMCs in a resistance artery or arteriole, *in vivo*, is particularly challenging. Pharmacological approaches that are so useful in a patch clamp experiment, where specific currents can be readily identified, are problematic in a complex tissue because of expression of similar channels in multiple cell types as well as the complex pattern of expression of ion channels within SMCs. The use of blockers in the absence of electrophysiological characterization of the repertoire of channel currents expressed within SMCs is particularly problematic because of the lack of selectivity of most ion channel blockers (Table 2). This situation is compounded, *in vivo*, where multiple cell types interact and where the site of action of a drug cannot be established. The use of cell specific, conditional knockout and knockin models can help resolve some of these issues, but given the complex interactions among proteins in signaling complexes, even this approach can be a relatively blunt tool to use *in vivo* without detailed electrophysiological characterization of the cell in question. The bottom line is, that if you want to understand the function of a given ion channel, multiple approaches should be applied and should always include patch clamp studies characterizing the currents through the channels in question.

As pointed out repeatedly, there is considerable heterogeneity in the spectrum of ion channels expressed in vascular SMCs in different vascular beds and at different levels of the circulation within a given vascular bed. With the exception of rat mesenteric arteries, rat cerebral arteries, and mouse mesenteric arteries where there is extensive knowledge of the spectrum of ion channels expressed as well as their function, there are only bits and pieces of information available for other vessels, particularly for SMCs in arterioles in the microcirculation around the body. The microvasculature deserves more study in the future.

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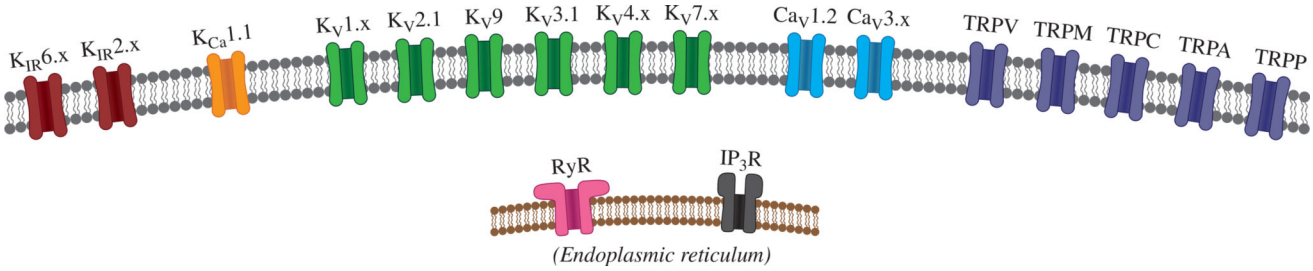

Figure 1.

Principal ion channels expressed in vascular SMCs. In the plasma membrane (gray), the following channels are expressed: at least two members of the inward-rectifier K^+ channel (K_{IR}) family; large-conductance, Ca^{2+}-activated K^+ channels (K_{Ca} 1.1); at least six members of the voltage-dependent K^+ channel (K_v) family; at least two voltage-dependent Ca^{2+} channels (Ca_v); and a number of TRP channels. In the endoplasmic reticular membrane (brown), RyRs and IP_3R are expressed.

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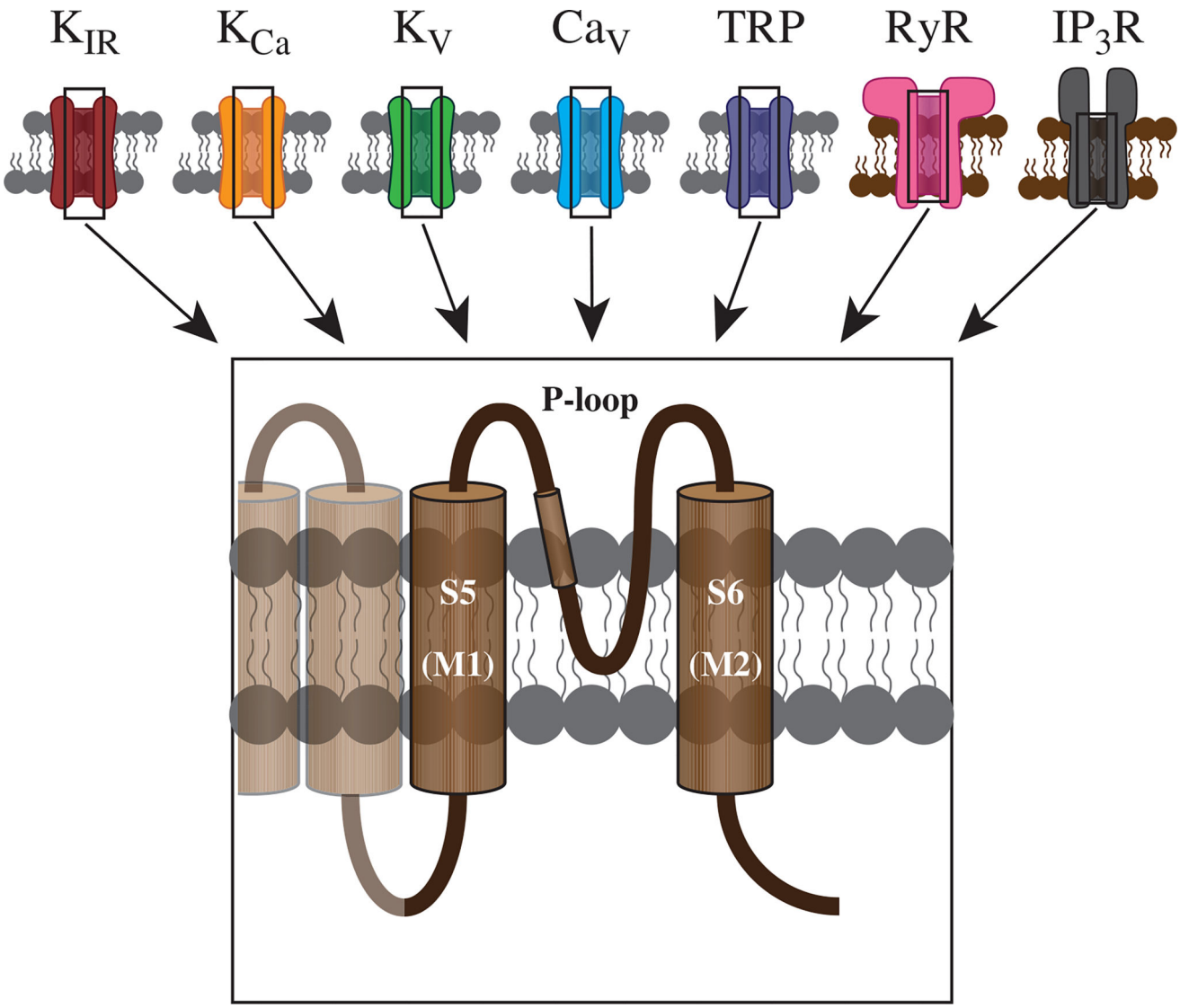

Figure 2.

Pore-forming subunits of ion channels. All ion channels share a similar topology, wherein the S5 and S6 transmembrane domains (M1 and M2 for K_{IR} channels) form the ion-permeable pore. These two domains are linked by a pore-loop (P-loop), which contains multiple residues responsible for regulating pore function and ion selectivity. See text for details.

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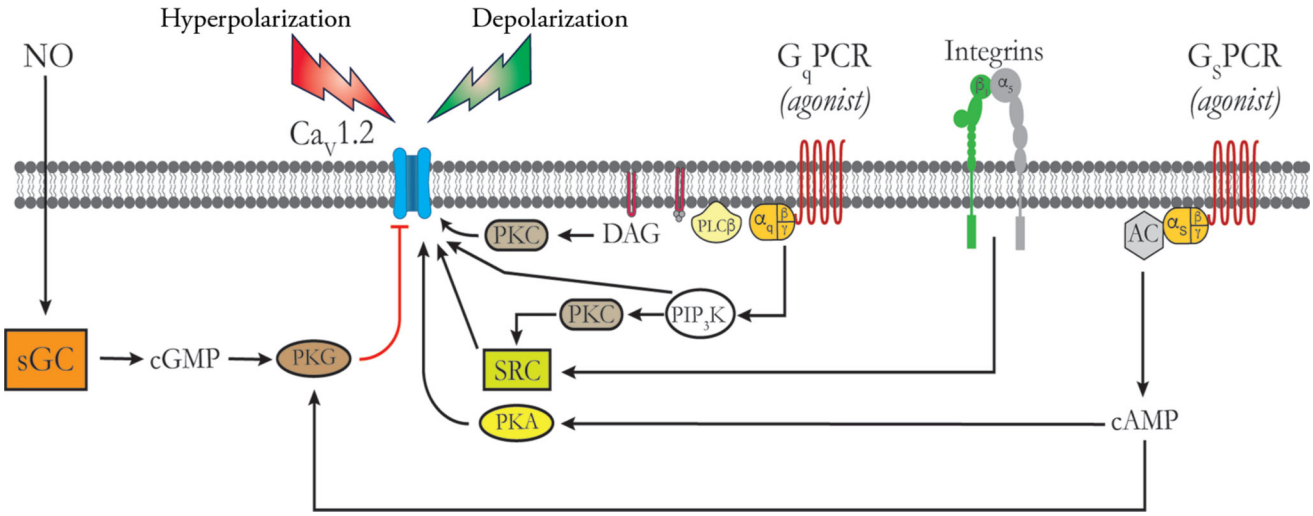

Figure 3.

Regulation of Ca_V 1.2 channels by vasoconstrictors and vasodilators. Schematic of the plasma membrane of a vascular SMC showing, from left to right, a Ca_V 1.2 channel, a G_q-protein coupled receptor (G_qPCR), an α5β1 Integrin and a G_s-protein coupled receptor (G_SPCR). Black lines and arrows indicate stimulation, activativation or increases; red lines indicate inhibition. Pathways to the right of the Ca_V 1.2 activate these channels, while those to the left are inhibitory. Membrane depolarization due to opening of membrane channels that conduct Na^+, Ca^{2+}, or Cl^- or due to closue of K^+ channels represents the major stimulus for opening Ca_V 1.2 channels. Vasoconstictor agonists that act through G_qPCRs norepinephrine, endothelin, angiotensin II, 5-HT, etc.) are coupled to phospholipase Cβ (PLCβ), which acts on q membrane phophoinositol bisphosphate to form diacylglycerol (DAG), which, in the presence of Ca^{2+}, activates PKC. PKC phosphorylates Ca_V 1.2 to increase its open-state probability. G_qPCR activation can also stimulate phosphatidyl inostitol trisphosphate kinase (PIP_3K), which acts on novel PKCs to activate the tyrosine kinase SRC, as shown. SRC phosphorylates Ca_V 1.2 channels, increasing their activity. Activation of Ca_V 1.2 by PIP_3K independent of PKC and SRC has also been reported. SRC can also be activated by activated inetgrins as shown, also increasing Ca_V 1.2 activity. Agonists for G_sPCR (isoproterenol, adenosine, prostacyclin, CGRP, etc.) activate adenylate cyclase (AC) to increase the formation of cAMP which activates PKA. PKA phosphorylates Ca_V 1.2 to increase the activity of this channel. Membrane hyperpolarization due to opening of K^+ channels or closure of channels conducting Na^+, Ca^{2+}, or Cl^- represents the main stimulus for deactivation of Ca_V 1.2 channels. In addition, nitric oxide (NO) acting through soluble guanylate cyclase (sGC), and other agents that increase cGMP, activate protein kinase G (PKG) which can phosphorylate Ca_V 1.2 channels to decrease their activity. In addition, high levels of cAMP can transactivate PKG accounting for the inhibitory effects of high levels of activation of G_sPCR or direct activators of AC such as forskolin on Ca_V 1.2 channel activity. See text for details and references.

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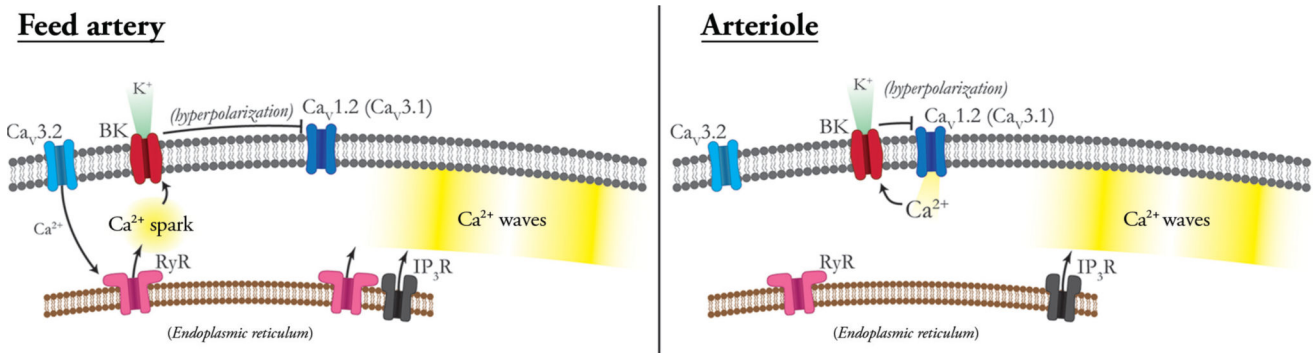

Figure 4.

Calcium signaling in feed arteries *versus* downstream arterioles. Feed arteries display both Ca^{2+} sparks and Ca^{2+} waves, as shown. Ca^{2+} sparks in feed arteries arise from RyRs that may be activated by Ca^{2+} influx through Ca_V 3.2 channels via Ca^{2+}-induced Ca^{2+} release. In feed arteries, Ca^{2+} sparks activate BK_{Ca} channels, hyperpolarizing the membrane and deactivating Ca_V 1.2 channels, which contributes to the negative feedback regulation of myogenic tone. Ca^{2+} waves in feed arteries depend on the activity of both RyRs and IP_3Rs. In arterioles, Ca^{2+} influx through Ca_V 1.2 and other VGCCs provides the Ca^{2+} signal for activation of BK_{Ca} channels and the negative feedback regulation of membrane potential and VGCC activity. Ca^{2+} waves in arterioles depend solely on the activity of IP_3R. RyRs are expressed in arteriolar SMCs but are silent under resting conditions. See text for details.

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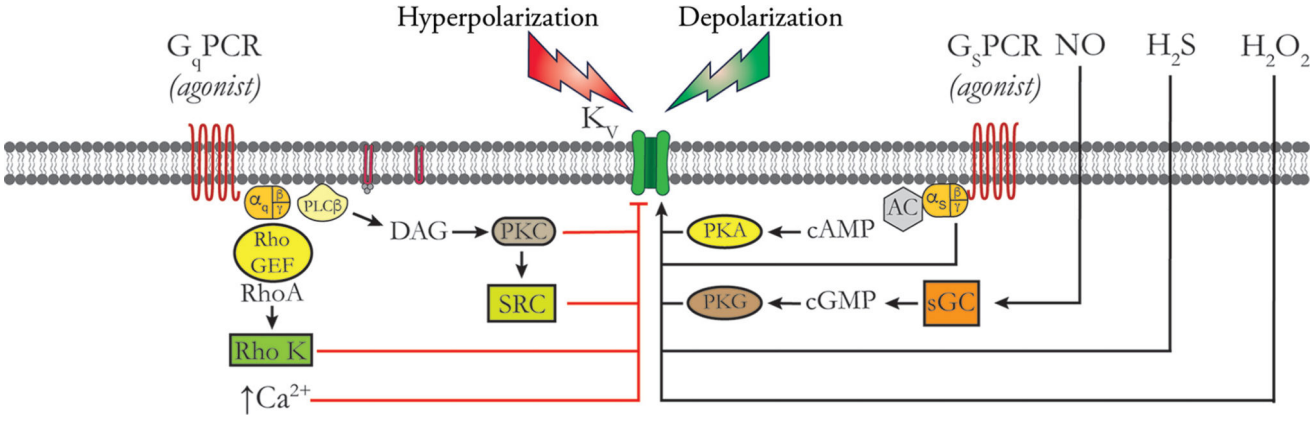

Figure 5.

Regulation of K_V channels by vasoconstrictors and vasodilators. Schematic of the plasma membrane of a vascular SMC showing, from left to right, a G_q-protein-coupled receptor (G_qPCR), associated G-proteins and phospholipase C-β (PLCβ); a generic K_V channel; and a G_s-protein-coupled receptor, associated G-proteins and adenylate cyclase (AC). Black lines and arrows indicate stimulation, activation or increases; red lines indicate inhibition. Pathways to the right of the K_V channel activate these channels, while those to the left are inhibitory. Membrane depolarization due to opening of membrane channels that conduct Na^+, Ca^{2+}, or Cl^- or due to closure of other K^+ channels represents the major stimulus for opening K_V channels. Vasodilator agonists that act at G_sPCR (isoproterenol, adenosine, prostacyclin, CGRP, etc.), stimulate the formation of cAMP, activation of PKA and phosphorylation of K_V channels leading to their activation. In addition, the $G_{\beta\gamma}$-subunits can directly interact with some K_V channels also leading to their activation. NO, acting through sGC, and other vasodilators that stimulate the production of cGMP, activeate PKG, phosphorylating K_V channels and increasing their activity. Other vasodilators, such as H_2S and H_2O_2 also can activate K_V channels as shown. Hyperpolarization, induced by opening of other K^+ channels or closure of channels conducting Na^+, Ca^{2+}, or Cl^-, represents the major stimulus for closure of K_V channels. In addition, vasoconstrictors that act through Gq-coupled receptors can inhibit K_V channels through several mecahisms including: (A) the activation of PLCβ, the formation of DAG and activation of PKC; (B) PKC-dependent activation of the tyrosine kinase SRC; (C) Rho-guanine-nuclotide exchange factor (Rho-GEF)-dependent activation of RhoA and Rho kinase (Rho K); and (D) agonist-induced increases in intracellular Ca^{2+}. See text for more information.

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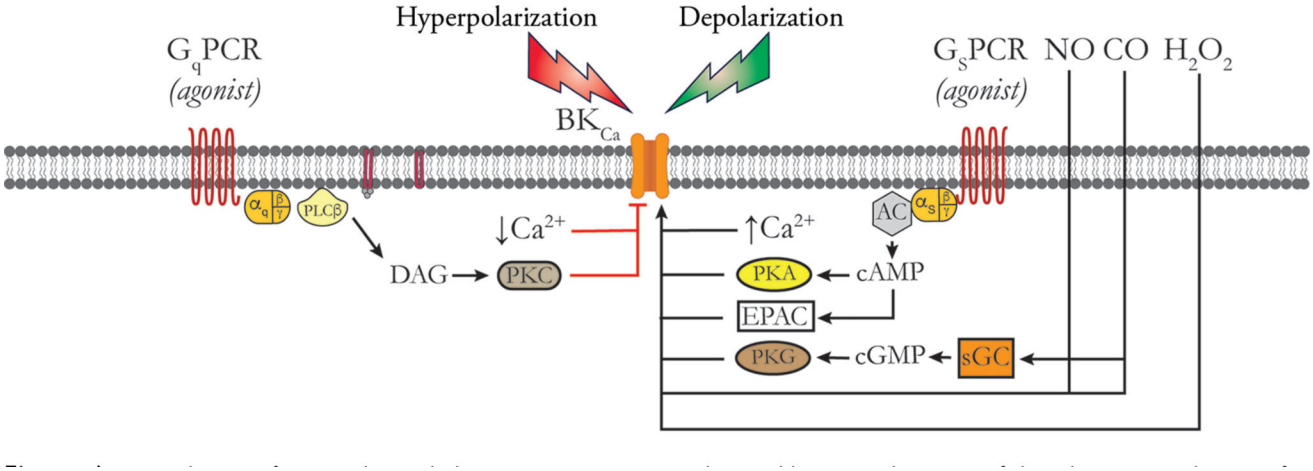

Figure 6.

Regulation of BK_{Ca} channels by vasoconstrictors and vasodilators. Schematic of the plasma membrane of a vascular SMC showing, from left to right, a G_q-protein-coupled receptor (G_qPCR), associated G-proteins and PLCβ; a BK_{Ca} channel; and a G_s-protein-coupled receptor, associated G-proteins and AC. Black lines and arrows indicate stimulation, activation or increases; red lines indicate inhibition. Pathways to the right of the BK_{Ca} channel activate these channels, while those to the left are inhibitory. Membrane depolarization due to opening of membrane channels that conduct Na^+, Ca^{2+}, or Cl^- or due to closure of other K^+ channels as well as increases in subsarcolemmal Ca^{2+} are the major stimulae for opening BK_{Ca} channels. Vasodilator agonists that act at G_sPCR (isoproterenol, adenosine, prostacyclin, CGRP, etc.), stimulate the formation of cAMP, activation of PKA and phosphorylation of BK_{Ca} channels leading to their activation. Vasodilators that lead to increased production of cAMP als may active BK_{Ca} channels through exchange EPACs. NO, acting through sGC, and other vasodilators that stimulate the production of cGMP, activate PKG, phosphorylating BK_{Ca} channels and increasing their activity. Other vasodilators, such as H_2S and H_2O_2 also can activate K_V channels as shown. NO or carbon monoxide (CO) also may directly interact with BK_{Ca} channels or associated heme-proteins to increase channel activity. BK_{Ca} channels also are activated by H_2O_2. Conversely, hyperpolarization, induced by opening of other K^+ channels or closure of channels conducting Na^+, Ca^{2+}, or Cl^-, and/or a fall in subsarcolemmal Ca^{2+} represent the major stimulae for closure of K_V channels. In addition, vasoconstrictors that act through Gq-coupled receptors can inhibit BK_{Ca} channels through activation of PLCβ, the formation of diacylglycerol (DAG) and activation of PKC. See text for more information.

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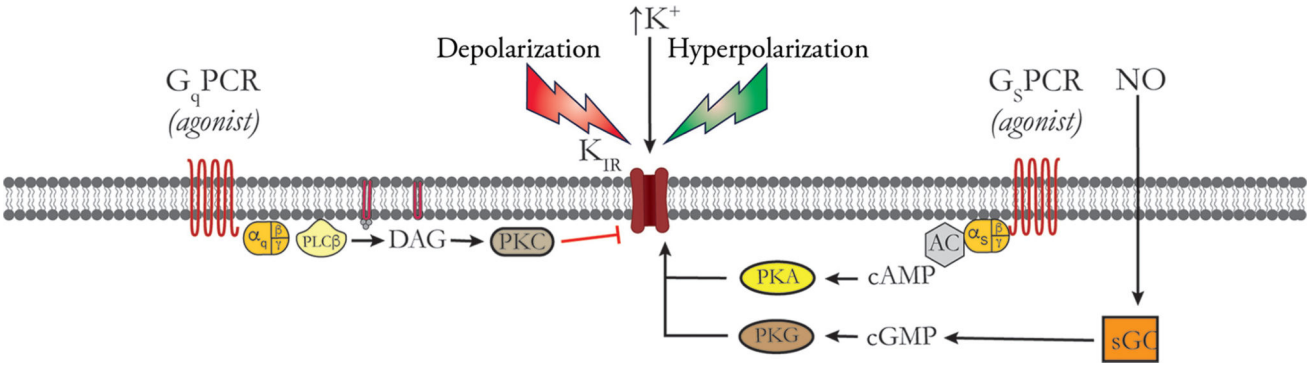

Figure 7.

Regulation of K_{IR} channels by vasoconstrictors and vasodilators. Schematic of the plasma membrane of a vascular SMC showing, from left to right, a G_q-protein-coupled receptor (G_qPCR), associated G-proteins and PLCβ; a K_{IR} channel; and a G_s-protein-coupled receptor, associated G-proteins and AC. Black lines and arrows indicate stimulation, activation or increases; red lines indicate inhibition. Hyperpolarization induced by the activation of other K^+ channels, or the closure of channels conducting Na^+, Ca^{2+}, or Cl_- and/or increases in extracellular K^+ concentration are the major stimuli for activation of vascular SMC K_{IR} channels. In addition, vasodilators that act at G_sPCRs (isoproterenol, adenosine, prostacyclin, CGRP, etc.), stimulate AC, increase the production of cAMP and activate PKA lead to activation of K_{IR} channels. Similarly, NO, acting through sGC to increase production of cGMP, activated protein kinase G which can activate K_{IR} channels. Conversely, membrane depolarization due to closure of other K^+ channels or opening of channels that conduct Na^+, Ca^{2+}, or Cl_- will close K_{IR} channels. Vasoconstrictors that act through G_qPCRs (norepinephrine, endothelin, angiotensin II, 5-HT, etc.) to activate PLCβ, the production of DAG and PKC activation lead to closure of K_{IR} channels. See text for more information.

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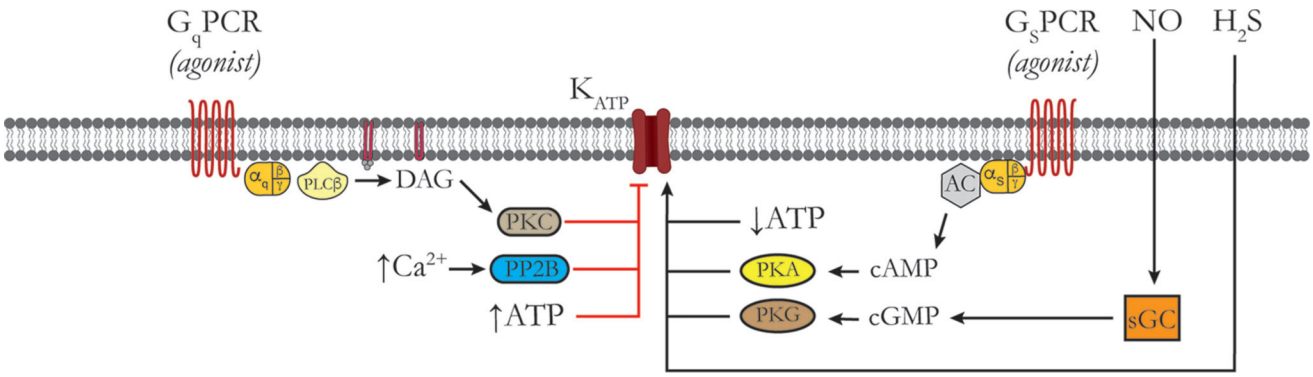

Figure 8.

Regulation of K_{ATP} channels by vasoconstrictors and vasodilators. Schematic of the plasma membrane of a vascular SMC showing, from left to right, a G_q-protein-coupled receptor (G_qPCR), associated G-proteins and PLCβ; a K_{ATP} channel; and a G_s-protein-coupled receptor, associated G-proteins and AC. Black lines and arrows indicate stimulation, activation or increases; red lines indicate inhibition. These channels can be activated by a fall in intracellular ATP in the environment of these channels. In addition, vasodilators that act at G_SPCRs (isoproterenol, adenosine, prostacyclin, CGRP, etc.), stimulate AC, increase the production of cAMP and activate PKA lead to activation of K_{ATP} channels. Similarly, NO, acting through sGC to increase production of cGMP, activating PKG which can activate K_{ATP} channels. These channels also can be activated by H_2S, as shown. Conversely, increases in ATP close K_{ATP} channels. Vasoconstrictors that act through G_qPCRs (norepinephrine, endothelin, angiotensin II, serotonin, etc.) to activate PLCβ, the production of DAG and PKC activation will lead to closure of K_{IR} channels. Increases in intracellular Ca^{2+} that accompany SMC stimulation by vasoconstrictors activates protein phosphatase 2B (calcineurin), which also closes K_{ATP} channels by dephosphorylation. See text for more information.

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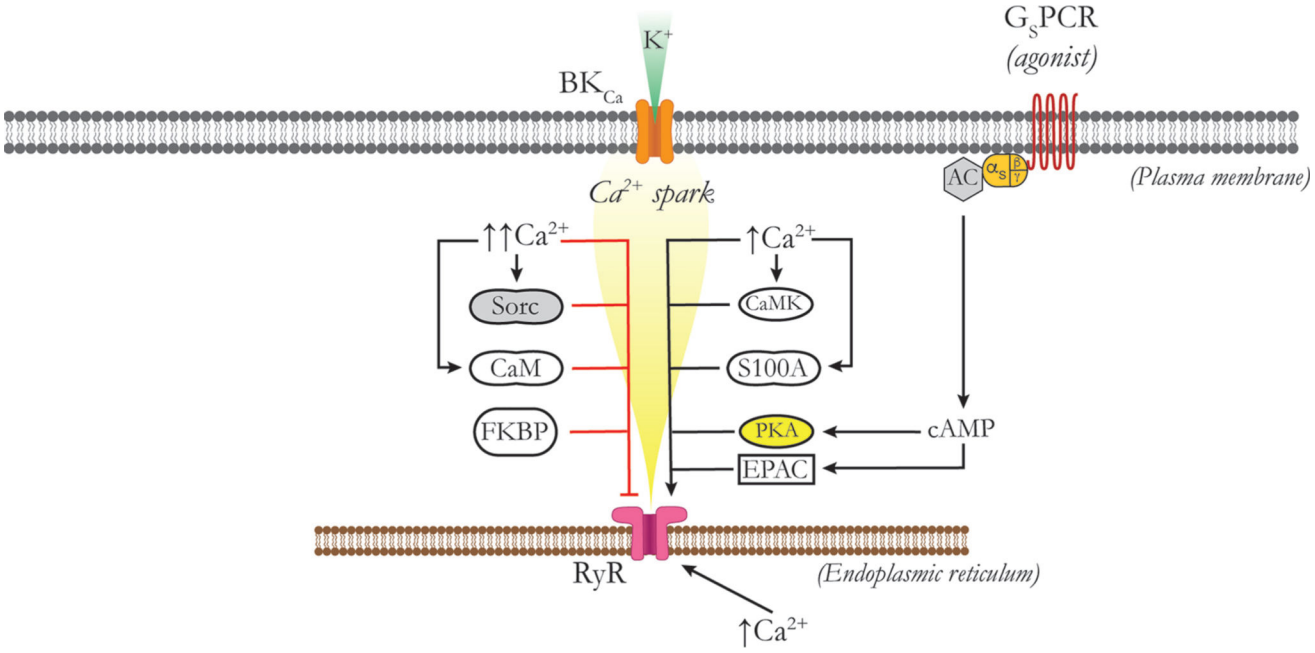

Figure 9.

Regulation of RyRs. Schematic of the plasma membrane and the ER membrane of a vascular SMC showing, from left to right in the plasma membrane, a BK_{Ca} channel and a G_s-protein-coupled receptor, associated G-proteins and AC, and a RyR in the membrane of the ER. Moderate increases in cytoplasmic Ca^{2+} in the environment of a RyR, or increases in the concentration of Ca^{2+} in the lumen of the ER are the primary stimulae for activation of RyRs. Activation of RyR by cytosolic Ca^{2+} is mediated by direct actions of Ca^{2+} on the channels, through activation of calcium-calmodulin-dependent protein kinase (CaMK) and phosphorylation of the channels, or interactions of Ca^{2+} with the Ca^{2+}-binding protein S100A which competes with calmodulin for binding to the RyR. Vasodilators that act at G_sPCRs (isoproterenol, adenosine, prostacyclin, CGRP, etc.), activate AC to increase production of cAMP which then can activate PKA to phosphorylate RyRs and increase their activity increasing the frequency of production of Ca^{2+} sparks. Elevated cAMP can also increase RyR activity through activation of EPACs. The increase in RyR-depedent Ca^{2+} spark activity is transduced into membrane hyperpolarization and vasodilation through activation of overlying BK_{Ca} channels, as shown. Conversely, high levels of intracellular Ca^{2+} inhibit RyR activity through mechanisms involving the Ca^{2+}-binding proteins sorcin (SORC) or calmodulin (CaM). The activity of RyRs also may be decreased by interactions with FK-506 binding proteins 12 and 12A FKBPs. See text for more information.

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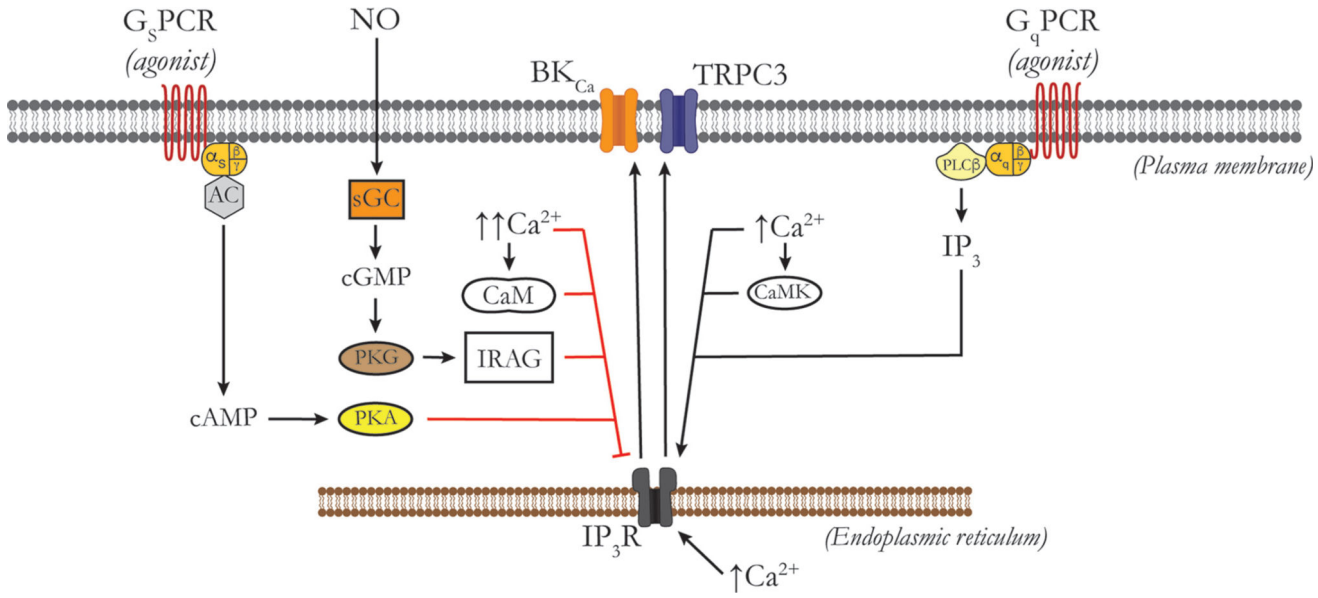

Figure 10.

Regulation of IP_3 receptors by vasoconstrictors and vasodilators. Schematic of the plasma membrane and the ER membrane of a vascular SMC showing, from left to right in the plasma membrane, a G_s-protein-coupled receptor, associated G-proteins and AC, a BK_{Ca} channel, a TRPC3 channel and a G_q-protein-coupled receptor (G_qPCR), associated G-proteins and phospholipase C-β (PLCβ), and an IP_3 receptor (IP_3R) in the membrane of the ER. Increases in IP_3 and moderate increases in cytoplasmic Ca^{2+} in the environment of an IP_3R are the primary stimulae for activation. Activation of IP_3Rs by cytosolic Ca^{2+} is mediated by direct actions of Ca^{2+} on the channels, or through activation of calcium-calmodulin-dependent protein kinase (CaMK) and phosphorylation of the channels. Vasoconstrictors acting through G_qPCRs and activation of PLCβ increase the production of IP_3, stimulating Ca^{2+} release through IP_3R. Activated IP_3Rs have been shown to physically interact with, and activate plasma membrane BK_{Ca} and TRPC3 channels, as shown. Conversely, high levels of intracellular Ca^{2+} inhibit IP_3R activity through mechanisms involving the Ca^{2+} binding protein, CaM. NO, through activation of soluble guanylate cyclase, increased production of cGMP and activation of PKG phosphorylates IRAG which inhibits IP_3R activity. Vasodilators that act at G_sPCRs (isoproterenol, adenosine, prostacyclin, CGRP, etc.), activate AC to increase producting of cAMP which then can activate PKA to phosphorylate IP_3Rs to decrease their activity. See text for more information.

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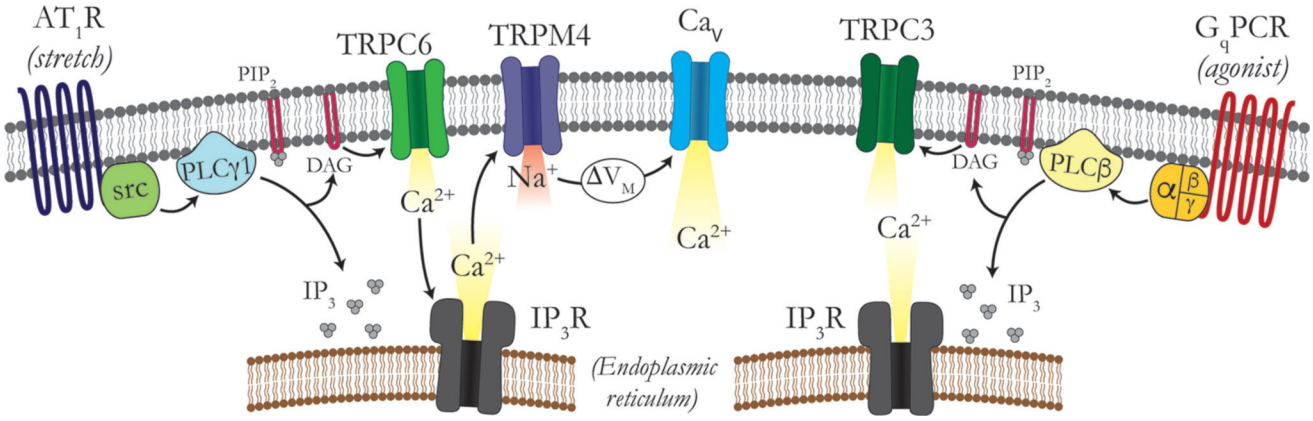

Figure 11.

TRP channel regulation of myogenic and agonist-induced smooth muscle contractility. Increased intravascular pressure activates a stretch-sensitive G_q-protein-coupled-receptor (G_qPCR; e.g., angiotensin type 1 receptor, AT_1R), which then causes the hydrolysis of PIP_2 by phospholipase C- γ1 (PLCγ1) to form DAG and IP_3. DAG activates TRPC6 channels to increase cytosolic Ca^{2+} concentration, combined with IP_3-mediated Ca^{2+} release through IP_3Rs in the ER. This local increase in cytosolic Ca^{2+} concentration activates TRPM4-dependent Na^+ influx, membrane depolarization, and opening of Ca_v 1.2 channels. This results in SMC contraction (myogenic tone). A similar mechanism is activated in response to a G_qPCR agonist, through activation of PLCβ and TRPC3 channels. Figure adapted, with permission, from Earley and Brayden (361). See text for more information.

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Table 1

Vascular Voltage-Gated Ca^{2+} Channels and Their Pharmacology

Channel	Gene	Alternative names	Accessory subunits	Inhibitors/antagonists (IC_{50})	Activators/agonists (EC_{50})
Ca_V 1.2	CACNA1C	L-type	β_2 and β_3, $\alpha_2\delta_1$	Nifedipine (10–100 nmol/L) (872)	BayK 8644 (6 nmol/L) (1638)
				Nimodipine (139 nmol/L) (1563)	FPL64176 (211 nmol/L) (1638)
				Diltiazem (500 nmol/L) (615)	
				Verapamil (60 nmol/L) (615)	
				Mibefradil (1.4–13 μmol/L) (576, 948)	
				Cd^{2+} (7 μmol/L) (1054)	
				Ni^{2+} (280 μmol/L) (1054)	
				Kurtoxin (> 10 μmol/L) (251)	
				ML218 (> 10 μmol/L) (1560)	
Ca_V 3.1	CACNA1G	T-type, α1G		Mibefradil (0.4–1.2 μmol/L) (576)	
				Cd^{2+} (160 μmol/L) (833)	
				Ni^{2+} (167–250 μmol/L) (833)	
				Kurtoxin (15 nmol/L) (251)	
				ML218 (~300 nmol/L) (1560)	
Ca_V 3.2	CACNA1H	T-type, α1H		Mibefradil (1.1–1.2 μmol/L) (576)	
				Cd^{2+} (160 μmol/L) (833)	
				Ni^{2+} (5.7–12 μmol/L) (833)	
				Kurtoxin (61 nmol/L) (251)	
				ML218 (310 nmol/L) (1560)	

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Table 2

Vascular K^+ Channels and Their Pharmacology

Channel	Gene	Alternative names	Accessory subunits	Inhibitors/antagonists (IC_{50})	Activators/agonists (EC_{50})
K_V 1.1	KCNA1		K_V β1, K_V β2	TEA (0.3 mmol/L) (504)	
				4-AP (0.29 mmol/L) (504)	
				correolide (430 nmol/L) (414)	
				α-dendrotoxin (20 nmol/L) (504)	
				dendrotoxin-k (2.5 nmol/L) (1208)	
				hongotoxin (31 pmol/L) (783)	
				margatoxin (144 pmol/L) (783)	
				kaliotoxin (41 nmol/L) (504)	
				ShK toxin (16 pmol/L) (723)	
				Psora-4 (62 nmol/L) (1472)	
				PAP-1 (65 nmol/L) (1267)	
K_V 1.2	KCNA2		K_V β1, K_V β2	TEA (0.56 μmol/L) (504)	
				4-AP (0.59 mmol/L) (504)	
				correolide (700 nmol/L) (414)	
				charybdotoxin (14 nmol/L) (504)	
				α-dendrotoxin (17 nmol/L) (504)	
				hongotoxin (170 pmol/L) (783)	
				margatoxin (675 pmol/L) (783)	
				ShK toxin (9 nmol/L) (723)	
				Psora-4 (49 nmol/L) (1472)	
				PAP-1 (250 nmol/L) (1267)	
K_V 1.3	KCNA3		K_V β2	TEA (10 mmol/L) (504)	
				4-AP (0.195 mmol/L) (504)	
				correolide (86 nmol/L) (414)	
				α-dendrotoxin (250 nmol/L) (504)	
				dendrotoxin-k (2.5 nmol/L) (1208)	
				hongotoxin (86 pmol/L) (783)	
				margatoxin (230 pmol/L) (783)	

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Channel	Gene	Alternative names	Accessory subunits	Inhibitors/antagonists (IC_{50})	Activators/agonists (EC_{50})
				kaliotoxin (0.65 nmol/L) (504)	
				ShK toxin (11 pmol/L) (723)	
				Psora-4 (3 nmol/L) (1472)	
				PAP-1 (2 nmol/L) (1267)	
K_V 1.5	KCNA5		K_V β1.2, K_V	TEA (330 mmol/L) (504)	
			β2, K_V β3	4-AP (0.27 mmol/L) (504)	
				correolide (1.1 μmol/L) (414)	
				Psora-4 (7.7 nmol/L) (1472)	
				PAP-1 (45 nmol/L) (1267)	
K_V 1.6	KCNA6		K_V β1, K_V β2	TEA (1.7–7 mmol/L) (485, 509, 754)	
				4-AP (0.3–1.5 mmol/L) (509, 754)	
				correolide (450 nmol/L) (414)	
				charybdotoxin (1 nmol/L) (509)	
				α-dendrotoxin (25 nmol/L) (754)	
				hongotoxin (6 nmol/L) (783)	
				margatoxin (144 pmol/L) (783)	
				ShK toxin (165 pmol/L) (723)	
				PAP-1 (62 nmol/L) (1267)	
K_V 2.1	KCNB1		K_V 9.3	TEA (4.9 mmol/L) (575)	
				4-AP (18 mmol/L) (755)	
				Ba^{2+} (30 mmol/L) (1369)	
				SsmTx-1 (41.7 nmol/L) (230)	
				stromotoxin-1 (12.7 nmol/L) (387)	
				PAP-1 (3 μmol/L) (1267)	
K_V 3.1	KCNC1			TEA (0.2 mmol/L) (504)	
				4-AP (29 μmol/L) (504)	
				PAP-1 (5 μmol/L) (1267)	
K_V 4.1	KCND1			TEA (11 mmol/L) (1324)	
				4-AP (1 mmol/L) (1324)	
				phrixotoxin 1 (>250 nmol/L) (335)	

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Channel	Gene	Alternative names	Accessory subunits	Inhibitors/antagonists (IC_{50})	Activators/agonists (EC_{50})
				phrixotoxin 2 (>300 nmol/L) (335)	
K_V 4.2	KCND2			TEA (11 mmol/L) (1324)	
				4-AP (1 mmol/L) (1324)	
				phrixotoxin 1 (5 nmol/L) (335)	
				phrixotoxin 2 (34 nmol/L) (335)	
				PAP-1 (1.2 μmol/L) (1267)	
K_V 4.3	KCND3			TEA (~11 mmol/L) (1324)	
				4-AP (1.2 mmol/L) (1380)	
				phrixotoxin 1 (28 nmol/L) (335)	
				phrixotoxin 2 (71 nmol/L) (335)	
K_V 7.1	KCND4		KCNE1–5	TEA (5 mmol/L) (1205)	ML277 (0.26 μmol/L) (964)
				Linopirdine (40 μmol/L) (1102)	ML213 (>10 μmol/L) (1609)
				XE991 (0.8 μmol/L) (1205)	R-L3 (L-364, 373; <1 μmol/L) (1236)
				Chromanol 293B (0.5–63 μmol/L) (130)	
				HMR-1556 (120 nmol/L) (481)	
				L735821 (173 nmol/L) (1275)	
				Retigabine (~100 μmol/L) (517)	
K_V 7.4	KCNQ4		KCNE1–5	TEA (3 mmol/L) (1205)	ML277 (>30 μmol/L) (964)
				Linopirdine (14 μmol/L) (1321)	ML213 (0.5–0.8 μmol/L) (179, 1609)
				XE991 (5.5 μmol/L) (1321)	Retigabine (5.3 μmol/L) (517)
K_V 7.5			KCNE1–5	XE991 (65 μmol/L) (1205)	Retigabine (6.4 μmol/L) (517)
					ML213 (700 nmol/L) (179)
K_V 9.3	KCNS3		K_V 2.1	See K_V 2.1 earlier	
K_{Ca} 1.1	KCNMA1	BK_{Ca}, Slo1	β1–4	Iberiotoxin (1.7 nmol/L) (1509)	NS1619 (1107)
			(KCNMB1–4)	Charybdotoxin (2.9 nmol/L) (1509)	BMS204352 (352 nmol/L) (500)
			LRRC26	Paxilline (1.9 nmol/L) (1509)	Dehydrosoyasaponin-I (DHS-I) (60 nmol/L) (476)
				TEA (0.14 mmol/L) (1509)	
				Psora-4 (5 μmol/L) (1472)	17β-Estradiol (2.6 μmol/L) (1454)
				PAP-1 (2.5 μmol/L) (1267)	
K_{Ca} 2.3	KCNN3	SK_{Ca} 3, SK3	Calmodulin	Apamin (10 nmol/L) (1509)	EBIO (87–600 μmol/L) (1554)

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Channel	Gene	Alternative names	Accessory subunits	Inhibitors/antagonists (IC_{50})	Activators/agonists (EC_{50})
				UCL1684 (9.5 nmol/L) (1509)	NS309 (120–900 nmol/L) (1554)
				TRAM-34 (20 μmol/L) (1554)	SKA-31 (3 μmol/L) (1554)
				Psora-4 (5 μmol/L) (1472)	
				PAP-1 (5 μmol/L) (1267)	
K_{Ca} 3.1	KCNN4	IK_{Ca} 1, IK1	Calmodulin	Charybdotoxin (5 nmol/L) (1554)	EBIO (24–80 μmol/L) (1554)
				Chlotrimazole (70 nmol/L) (1509)	NS309 (10–27 nmol/L) (1554)
				TRAM-34 (10–25 nmol/L) (1554)	SKA-31 (260 nmol/L) (1554)
				NS6180 (11 nmol/L) (1554)	
				Psora-4 (5 μmol/L) (1472)	
				PAP-1 (10 μmol/L) (1267)	
K_{IR} 2.1	KCNJ2			Ba^{2+} (2 μmol/L at −100 mV; 19–30 μmol/L at −40 mV) (26, 881)	Extracellular K^+ (3–20 mmol/L) (903)
				Intracellular Mg^{2+} and polyamines (594)	
				ML133 (1.9 μmol/L) (1496)	
				PAP-1 (15 μmol/L) (1267)	
K_{IR} 2.2	KCNJ12			Ba^{2+} (0.5 μmol/L at −100 mV; 9 μmol/L at −40 mV) (881)	Extracellular K^+ (3–20 mmol/L) (903)
				ML133 (2.9 μmol/L) (1496)	
				Intracellular Mg^{2+} and polyamines (594)	
K_{IR} 2.3	KCNJ4			Ba^{2+} (10.3 μmol/L at −100 mV; 70 μmol/L at −40 mV) (881)	Extracellular K^+ (3–20 mmol/L) (903)
				ML133 (4 μmol/L) (1496)	
				Intracellular Mg^{2+} and polyamines (594)	
K_{IR} 6.1	KCNJ8		SUR2b	Ba^{2+} (100 μmol/L) (154)	Diazoxide (32 μmol/L) (941)
				Glibenclamide (20–100 nmol/L) (1074, 1187)	Pinacidil (0.6 μmol/L) (941)
				Tolbutamide (350 μmol/L) (1187)	Levcromakalim (79 nmol/L) (941)
K_{IR} 6.2	KCNJ11		SUR2b	Ba^{2+} (100 μmol/L) (154)	Diazoxide (32 μmol/L) (941)
				Glibenclamide (20–100 nmol/L) (1074, 1187)	Pinacidil (0.6 μmol/L) (941)
				Tolbutamide (350 μmol/L) (1187)	Levcromakalim (79 nmol/L) (941)
				ML133 (7.7 μmol/L) (1496)	

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Table 3

Vascular RyRs and IP_3Rs and Their Pharmacology

Channel	Gene	Alternative names	Accessory subunits	Inhibitors/antagonists (IC_{50})	Activators/agonists (EC_{50})
RyR1	RYR1		See (425, 921) for list of interacting proteins	Ryanodine (> 10 μmol/L)[b] (1657)	Ryanodine (100 nmol/L-1 μmol/L) (1657)
				Tetracaine (100 μmol/L) (1657)	Caffeine (0.2–0.5 mmol/L) (1657)
RyR2	RYR2		See RyR1	See RyR1	See RyR1
RyR3	RYR3		See RyR1	See RyR1	See RyR1
IP_3R1	ITPR1		See (434) for list of interacting proteins	Ca^{2+} (1.3–52 μmol/L) (434)	Ca^{2+} (57–348 nmol/L) (434, 1485)
				Heparin (4.1 μg/mL) (1237)	IP_3 (34 nmol/L) (1237)
				Xestospongin C/D (358–844 nmol/L) (456)	Adenophostine A (4.5 nmol/L) (1237)
				2-Aminoethoxydiphenyl borate (2-APB) (42 μmol/L) (950)	
IP_3R2	ITPR2		See (434) for list of interacting proteins	Ca^{2+} (1.3–52 μmol/L)[a] (434)	Ca^{2+} (58 nmol/L) (1485)
				Heparin (22 μg/mL) (1237)	IP_3 (151 nmol/L) (1237)
				2-Aminoethoxydiphenyl borate (2-APB) (~100 μmol/L) (1237)	
IP_3R3	ITPR3		See (434) for list of interacting proteins	Ca^{2+} (0.3–39 μmol/L) (434)	Ca^{2+} (77 nmol/L) (434)
				Heparin (2.8 μg/mL) (1237)	IP_3 (219 nmol/L) (1237)
				2-Aminoethoxydiphenyl borate (2-APB) (> 100 μmol/L) (1237)	Adenophostine A (19.5 nmol/L) (1237)

[a] The inhibitory effect of Ca^{2+} on Ca^{2+} release through IP_3R depends on the concentration of IP_3 to which the channel is exposed. The values shown are for [IP_3] = 10–100 nmol/L for IP_3R1 (934) and 20 nmol/L to 10 μmol/L for IP_3R3 (935).

[b] Concentrations required to block the channel.

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Table 4

Vascular Transient Receptor Potential Channels and Their Pharmacology (259)

Channel	Physiological activation	Selectivity [ratio]	Inhibitors/antagonists [IC_{50}]	Activators/agonists [EC_{50}]
TRPC1	G_q signaling; SOCE with STIM1 (1078, 1238)	Ca^{2+}:Na^+ [~1:1] (1347)	La^{3+} [n.d.] (1347)	n.d.
			Gd^{3+} [n.d.] (1655)	
TRPC3	Diacylglycerols (612)	Ca^{2+}:Na^+ [1.6:1] (1654)	Gd^{3+} [0.1 μmol/L] (539)	OAG [n.d.] (612)
			La^{3+} [4 μmol/L] (539)	
			2-APB [10 μmol/L] (874)	
			BTP2 [0.3 μmol/L] (574)	
TRPC4	G_i signaling; protons (693, 1279)	Ca^{2+}:Na^+ [1.1:1] (1258)	Niflumic acid [n.d.] (773)	(−)-englerin A [11.2 nmol/L] (25)
			ML204 [3.2 μmol/L] (1002)	
TRPC5	G_q/G_i/G_o signaling; calpain cleavage (693, 721, 1258)	Ca^{2+}:Na^+ [1.8:1] (1258)	2-APB [20 μmol/L] (1568)	rosiglitazone [32 μmol/L] (932)
			KB-R7943 [1.3 μmol/L] (789)	Ca^{2+} [1 μmol/L] (507)
			Mg^{2+} [500 μmol/L] (1101)	genistein [n.a.] (1543)
TRPC6	Diacylglycerols; stretch (indirectly) (612, 1331)	Ca^{2+}:Na^+ [4.5:1] (647)	Gd^{3+} [1.9 μmol/L] (647)	OAG [n.d.] (612)
			La^{3+} [3.9 μmol/L] (647)	SLG [n.d.] (612)
			SKF96365 [3.9 μmol/L] (647)	SAG [n.d.] (612)
TRPV1	Depolarization; heat; protons (206, 823)	Ca^{2+}:Na^+ [9.6:1] (206)	Capsazepine [40 nmol/L] (979)	capsaicin [30 nmol/L] (1481)
			JNJ17203212 [16 nmol/L] (1365)	resiniferatoxin [4 nmol/L] (1310)
			AMG517 [1 nmol/L] (143)	anandamide [1.3 μmol/L] (1309)
TRPV2	Osmolarity/stretch; heat *(rodent)*; IGF-1 *(rodent)* (205, 731, 1067)	Ca^{2+}:Na^+ [2.9:1] (205)	Tranilast [10 μmol/L] (1081)	probenecid [3.9 μmol/L] (83)
			ruthenium red [0.6 μmol/L] (205)	Δ^9-THC [16 μmol/L] (1181)
			SKF96365 [n.d.] (720)	cannabidiol [79 μmol/L] (1181)
TRPV3	Depolarization; heat (1566)	Ca^{2+}:Na^+ [12.1:1] (1566)	17(R)-resolvin D1 [0.4 μmol/L] (84)	eugenol [2 mmol/L] (1562)
			2,2-di(phenyl)oxolane [8 μmol/L] (255)	carvacrol [4 μmol/L] (363)
				2-APB [25 μmol/L] (256)
TRPV4	Heat; mechanical stimuli; G_q signalling (994, 1345, 1501)	Ca^{2+}:Na^+ [6.9:1] (1482)	GSK2193874 [5 nmol/L] (1407)	4α-PDD [0.2 μmol/L] (1499)
			HC067047 [50 nmol/L] (392)	GSK1016790A [20 nmol/L] (1408)
			RN1734 [2.5 μmol/L] (1480)	5,6-EET [0.1 μmol/L] (1500)
TRPM4	Intracellular Ca^{2+} (824)	Ca^{2+}:Na^+ [< 0.001:1] (1088)	9-phenanthrol [20 μmol/L] (497)	BTP2 [8 nmol/L] (1378)
			flufenamic acid [2.5 μmol/L] (1445)	decavanadate [2 μmol/L] (1089)
			ATP [1 μmol/L] (1092)	PIP_2 [5 μmol/L] (1085)
TRPM8	Depolarization; cooling (1481)	Ca^{2+}:Na^+ [3.2:1] (980)	BCTC [0.8 μmol/L] (107)	Icilin [0.2 μmol/L] (48)
			M8-B [0.8 μmol/L] (38)	menthol [16 μmol/L] (107)
			PBMC [0.5 nmol/L] (767)	WS-12 [13 μmol/L] (1289)
TRPA1	Chemosensation (129, 1490)	Ca^{2+}:Na^+ [0.84:1] (1046)	Resolvin D2 [2 nmol/L] (1137)	AITC [10 μmol/L] (714)

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Channel	Physiological activation	Selectivity [ratio]	Inhibitors/antagonists [IC_{50}]	Activators/agonists [EC_{50}]
			A967079 [63 nmol/L] (227)	acrolein [5 μmol/L] (97)
			HC030031 [6.3 μmol/L] (983)	PF-4840154 [25 nmol/L] (1229)
TRPP1 *	Cilial mechanosensation; Development (1278)	Ca^{2+}:Na^{+} [6:1] (323)	SKF96365 [n.d.] (1148)	Calmidazolium [n.d.] (323)

* In this instance, “TRPP1” is used to describe the *Pkd2* gene product. Prior to 2014, this same gene product is often referred to as “TRPP2” or “PKD2” in the literature. For further clarification, see the Section titled, “Polycystin (TRPP) Channels.”

n.d. = not determined.