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K_V channels and the regulation of vascular smooth muscle tone

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Abstract

Objective—The objective of this brief review is to provide an overview of the expression and function of K_V channels in VSMC of resistance arteries and arterioles.

Methods and Results—A review of the literature revealed that arterioles and resistance arteries express a diverse array of K_V channels with members of the K_V1, K_V2 and K_V7 families being particularly important. Members of the K_V channel family: 1.) are highly expressed in VSMCs; 2.) are active at the resting membrane potential of VSMCs in vivo (-45 to −30 mV); 3.) contribute to the negative feedback regulation of VSMC membrane potential and myogenic tone; 4.) are activated by cAMP-related vasodilators, hydrogen sulfide and hydrogen peroxide; 5.) are inhibited by increases in intracellular Ca^{2+} and vasoconstrictors that signal through G_q-coupled receptors; 6.) are involved in the proliferative phenotype of VSMC; and 7.) are modulated by diseases such as hypertension, obesity, the metabolic syndrome and diabetes.

Conclusions—K_V channels participate in every aspect of the regulation of VSMC function in both health and disease.

Keywords

K_V channels; potassium channels; vascular smooth muscle; resistance arteries; arterioles; vasoconstriction; vasodilation; microcirculation; blood flow

Introduction

Arterioles in the microcirculation contribute to vascular resistance and control of blood pressure and blood flow to and within tissues and organs [47]. Vascular smooth muscle cells (VSMCs) are the effectors of changes in vascular resistance; their contraction state, or tone, determines arteriolar internal diameters that strongly impacts the hydraulic resistance offered by these microvessels. Arteriolar tone, in turn, depends on VSMC intracellular Ca^{2+} concentration ($[Ca^{2+}]_{in}$) and the Ca^{2+} sensitivity of the VSMC contractile proteins [108]. The electrical potential across the plasma membrane (membrane potential) of VSMCs importantly impacts arteriolar tone by controlling the activity of voltage-gated Ca^{2+} channels (VGCC), a major source of activator Ca^{2+} in these microvessels [146]. Membrane potential also modulates Ca^{2+} release from internal stores and the Ca^{2+} sensitivity of the contractile machinery [48,57–59,117,122,132,154,186,191–193]. Thus, understanding the

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regulation of VSMC membrane potential is central to understanding the regulation of arteriolar tone and hence, blood pressure and blood flow control.

Potassium channels in VSMC plasma membranes play an important role in the control and regulation of VSMC membrane potential and arteriolar tone. They are the dominant plasmalemmal ion conductance in VSMCs, as in all cells, and their activity is modulated by membrane potential, vasodilators and vasoconstrictors such that these ion channels participate in all aspects of the regulation of arteriolar tone and control of microvascular perfusion [184]. At physiological ion concentrations (4–5 mM K^+ extracellular, 140 mM K^+ intracellular), the driving force (the electrochemical gradient) for diffusion of K^+ through K^+ channels is outward at physiological membrane potentials (-45 to −30 mV [22,53,112,169,188]). Thus, opening of K^+ channels leads to membrane hyperpolarization and vasodilation, whereas closure of K^+ channels results in membrane depolarization and vasoconstriction (Figure 1). Furthermore, because the membrane resistance of VSMCs is high (~1–10 GΩ [146]), only a few K^+ channels have to open or close to produce significant effects on membrane potential and arteriolar tone. Vascular SMCs express four or more classes of K^+ channels [184]. The remainder of this brief review will focus on voltage-gated K^+ (K_V) channels expressed by VSMCs and their role in the regulation of arteriolar and resistance artery tone and VSMC proliferation.

Discovery of K_V channels

Hodgkin and Huxley were the first to report currents through K_V channels using squid giant axons [80,81]. Currents through VSMC K_V channels were first reported by Beech and Bolton [13,14] and Okabe et al. [153] and confirmed by numerous investigators in every VSMC studied [39,66,87,89,96,131,147]. Membrane depolarization activates K_V channels; maintained depolarization results in a variable degree of channel inactivation [64,93,147]. However, K_V channel properties vary within and among tissues, suggesting diversity of expressed channels [64,70,93,147]. This functional diversity reflects molecular diversity of K_V channels and associated accessory subunits: there are 40 genes that code for mammalian K_V channels. This results in 12 distinct families of K_V channels (K_V1–12) [64,70]: Members of the K_V1–4, 7 and 10–12 form functional channels as homomers, whereas K_V5, 6, 8 and 9 must co-assemble with K_V2 or 3 subunits to form functional channels [64]. Vascular SMCs have been reported to express members of the K_V1 [39], K_V2 [39], K_V3 [39], K_V4 [39], K_V6 [145], K_V7 [66,96,131], K_V9 [39] and K_V11 [12] families of K_V channels, with K_V1, 2 and 7 being particularly important (see **K_V channels and myogenic tone**, below).

Structure of K_V channels

Functional K_V channels consist of homo- or heterotetramers of six transmembrane-domain (S1–S6), pore-forming α-subunits [64,93]. The pore of the channel is formed by the P-loop between S5 and S6 along with S6 from each α-subunit [11,64,92,116,147,156]. Positively charged amino acids in membrane spanning domain S4 detect changes in membrane potential and serve as the voltage sensor in these channels [11,64,92,116,147,156] (Figure 2). Fast, N-type inactivation involves the α-subunit N-terminus [82,83,92,116,196], whereas slow (C-type) inactivation involves the C-terminal domain and the channel's pore [83,116].

Accessory subunits interact with the pore-forming α-subunits and modulate channel function and interactions with scaffolding and other proteins in macromolecular signaling complexes [70,183]. Heterogeneity in the function of expressed K_V channels arises from the type of α-subunit(s) expressed, heteromultimerization of different α-subunits, the presence (or absence) of modifier subunits, alternative splicing and post-translational modifications [64,70].

Pharmacology of VSMC K_V channels

Pharmacological dissection of the function of individual K_V channels in VSMCs is challenging, because: 1.) VSMCs express a large number of K_V channel isoforms, and 2.) the pharmacology of K_V channels is diverse (Table 1). This difficulty is compounded in isolated vessel and in vivo experiments where the readout is only membrane potential, vessel diameter or isometric tension. Nonetheless, a pharmacological “finger print” of the functional expression of K_V channel isoforms can be established by the use of a combination of the more selective compounds, analysis of current kinetics in patch clamp experiments and functional assays using isolated vessels [41,42]. For example, Correolide, at micromolar concentrations [55], or psoralen derivatives (Psora-4 [187] and PAP-1 [167], Table 1) can be used to inhibit K_V 1 family members. While difficult to use in vivo, toxins, such as stromotoxin-1 (K_V 2.1) [54] or phrixotoxins (K_V 4) [51] can be used in patch clamp and isolated vessel experiments. There are a number of compounds that block various members of the K_V7 family (Table 1), and the availability of agonists for these channels provides a working armamentarium to study the function of this family of K_V channels. As with all drugs, care must be taken to use the lowest concentration possible to achieve channel blockade. For example, while PAP-1 is selective for K_V1 channels at nanomolar concentrations, this drug inhibits most other K_V channels at micromolar concentrations (Table 1).

K_V channels and myogenic tone

Early studies showed that: 1) 3,4-diaminopyridine or 4-aminopyridine (4-AP), which inhibit K_V1–4 channels [39], caused contraction of isolated VSMC in a number of isolated blood vessels [36,73,185], 2.) 4-AP inhibited currents around the resting membrane potential of rabbit portal vein myocytes and depolarized renal [60] and coronary [118] VSMCs, and 3.) 4-AP depolarized VSMCs and augmented myogenic tone at intraluminal pressures greater than 40 mm Hg in pressurized rabbit cerebral arteries [111]. Subsequent studies confirmed these findings in a number of arteries and arterioles [39,86–89,147] (Figure 3). These observations are consistent with the hypothesis that 4-AP-sensitive K_V channels contribute to VSMC resting membrane potential and to the negative feedback regulation of myogenic tone (Figure 1).

K_V1 channels in VSMCs

Members of the K_V1 family are expressed and contribute substantially to whole-cell K_V current in isolated VSMCs (~40% of whole-cell current at −40 mV [42]), resting VSMC membrane potential and the negative feedback regulation of myogenic tone [39,41,42,184]. Expression of K_V1.2, 1.5 and 1.6 appear to predominate with likely heteromerization among

these three isoforms [39,41,42,184]. Heteromeric K_V channels composed of K_V1.2, 1.5 and 1.6 have been proposed to underlie the delayed rectifier K_V channel currents of VSMCs in rabbit portal veins [104]. In rat mesenteric [42,127,158] and cerebral arteries [7] heteromers of K_V1.2 and K_V1.5 have been proposed. Herteromers consisting of K_V1.2 and K_V1.4 have been postulated to be expressed in rat renal arteries [56].

Expression of $K_V\beta$ subunits and their function with respect to K_V1 channels has only been examined in a few instances [39]. For example, rat retinal arteriolar SMCs display rapidly inactivating A-type K_V currents due to expression of K_V1.5 and accessory $K_V\beta$1 subunits [139,140]. These currents are in contrast to the slowly inactivating K_V currents that are displayed by most VSMCs (Figure 3A). Mouse coronary artery VSMCs express primarily $K_V\beta$1 and $K_V\beta$2 associated with K_V1.5 α-subunits, and that $K_V\beta$2 is required for normal trafficking of K_V1.5 α-subunits to the plasma membrane [150]. In rat mesenteric arteries, $K_V\beta$1.2 has been proposed to contribute to functional channel expression along with K_V1.2 and K_V1.5 [42].

Expression of transcripts for K_V1.3 has been detected in VSMCs of a number of arteries and arterioles [7,31,34,40,138,189,190], but not in all studies [30,56,181]. Despite the presence of mRNA transcripts for K_V1.3 in rat cerebral arteries, no protein was detected in lysates of these vessels [7]. Similarly, dialysis of VSMCs with K_V1.3 antibodies has no effect on whole-cell-K_V currents in cells from rat mesenteric artery [127]. In murine femoral artery VSMCs, currents through K_V1.3 channels account for only 11% of whole-cell K_V channel currents in native contractile VSMCs, but 58% of the current in proliferating VSMCs [34]. Furthermore, expression of K_V1.3 mRNA and protein was substantially elevated in proliferating VSMCs, and block of K_V1.3 with margatoxin or PAP-1 (Table 1) inhibited VSMC proliferation [34]. It is interesting to note that K_V1.3 channels participate in the phenotypic switch of contractile VSMCs to proliferating VSMCs through a mechanism that is independent of the K^+ flux-function of this protein [32,98], involves MEK/ERK and PLCγ signaling [33] and depends on the channel's COOH-terminus [98].

K_V2 channels in vascular SMCs

Vascular smooth muscle cells also express functional K_V2.1 channels [39,41,42,184] that contribute to whole cell K_V current (~20% at −40 mV [42]), resting membrane potential and the negative feedback regulation of myogenic tone [39,41,42,184]. Evidence from rat cerebral arteries [200] and rat mesenteric arteries [42] suggests that K_V2.1 may form heteromeric channels with K_V9.3. These heteromeric channels may be particularly important for regulation of VSMC resting membrane potential at low intravascular pressure [200]. In a hypertensive mouse strain, upregulation of the expression of K_V6.3 and its co-expression with K_V2 channels appears to account for decreased K_V2-based currents and membrane depolarization [145].

K_V3 and K_V4 channels in VSMCs

Expression of K_V3 and K_V4 mRNA has been reported in porcine coronary arterioles [77], rat mesenteric artery [189], and rat tail artery [190]. In rat mesenteric artery, while mRNA for K_V3 channel subunits was detected in whole-vessel lysates, expression of these K_V

channel subunits was not detected in isolated VSMCs [42]. These data suggest that K_V3 subunits may be expressed in some other cell-type found in the wall of these resistance arteries. Protein for $K_V3.2$ was not detected in rat mesenteric arteries [42,189]. Selective inhibitors of K_V3 and K_V4 channels have no effect on whole-cell currents in rat mesenteric arteries [42]. Thus, there appears to be little evidence for functional expression of these subunits related to the regulation of vascular tone. However, in human uterine arteries, $K_V3.4$ channels play a permissive role in VSMC proliferation [141,142].

K_V7 channels in VSMCs

Members of the K_V7 family also contribute to whole cell currents (20% at −40 mV [42]), resting membrane potential and the negative feedback regulation of myogenic and vasoconstrictor-induced tone in several vessels; $K_V7.4$ and 7.5 appear to play a major role [42,66,96,131]. Expression of the auxiliary subunit, KNCE4, is required for expression and function of VSMC $K_V7.4$ in rat mesenteric arteries [94] and confers sex-linked differences in $K_V7.4$ function and vascular reactivity in the mouse [1]. These channels also interact with G-protein βγ-subunits, that appear to be required for channel activity and which participate the in the regulation of myogenic tone in rat renal arteries [175].

K_V11 channels in VSMCs

In addition to $K_V1.3$ and $K_V3.4$ channels mentioned above, K_V11 channels also appear to participate in proliferation of VSMCs [12]. Transcripts and protein for $K_V11.1$ were detected in VSMCs of several murine arteries [12]. However, currents through these channels were only detected in VSMCs from portal vein, but not in VSMCs isolated from carotid arteries [12]. Nonetheless, an inhibitor of $K_V11.1$ channels, dofetilide (Table 1), suppressed, whereas an activator, NS1643 (Table 1), enhanced proliferation of VSMCs isolated from murine femoral arteries [12].

Vasoconstrictors and K_V channels

Vasoconstrictors that act at G-protein coupled receptors and depolarize VSMCs activate K_V channels [23,30,31,36,71,136,155,168]. This activation blunts the vasoconstriction and is part of the negative-feedback regulation of vascular tone, essentially preventing vasospasm. Membrane depolarization has also been shown to selectively traffic $K_V1.5$ channels to the plasma membrane of VSMCs, also contributing to the negative feedback regulation of VSMC membrane potential and vascular tone [107]. Nonetheless, there is evidence that K_V channel closure contributes to the mechanism of action of the same vasoconstrictors including phenylephrine [143], 5-HT [10,113,176] and angiotensin II [35]. These agents may act via protein kinases or by Ca^{2+}-mediated inhibition of K_V channels. Activation of protein kinases (PK) such as PKC [2,35,74,106,113], c-SRC [176], Rho-kinase [128,129] inhibits currents through 4-AP-sensitive K_V channels, contributing to vasoconstrictor-induced VSMC depolarization (Figure 3). Angiotensin II has been shown to selectively decrease the surface expression of $K_V1.5$ channels via PKC-dependent degradation of these K^+ channels [106]. Protein kinase C also inhibits K_V7 channels [131]. Agonist-induced increases in intracellular Ca^{2+} concentration also inhibit 4-AP-sensitive K_V channels [45,60,85]. Thus, agonist-induced activation of kinases and increases in intracellular Ca^{2+}

have the potential to close K_V channels, reduce their surface expression and provide a positive feedback signal to support depolarization, activation of VGCC and vasoconstriction (Figure 1).

Vasodilators and K_V channels

cAMP-PKA-mediated activation of K_V channels

Vasodilators that act through G_S-coupled receptors and the cAMP signaling cascade activate 4-AP-sensitive K_V channels (Figure 1) [3–5,17,49,52,76,78,119,165]. Protein kinase A phosphorylates $K_V1.2$ at serine 449 in the C-terminus to increase channel activity [99]. Vasodilators that act through the cAMP and cGMP signaling cascades also may act, in part, by antagonizing the Rho-kinase-mediated K_V channel downregulation [130]. In vessels where heteromers of $K_V1.2$ and 1.5 or 1.6 predominate [7,29,104,158,181], phosphorylation of $K_V1.2$ may underlie the 4-AP-sensitive effects of cAMP-PKA-related vasodilators. In rat cerebral artery VSMCs, PKA is targeted to $K_V1.2$ by the scaffolding protein PSD95, which binds to the COOH-terminus of these channels [144]. The beta receptor agonist, isoproterenol, and the adenylate cyclase activator, forskolin, activate $K_V7.4$ channels in renal VSMCs. Adenosine-induced dilation of coronary arteries [105] and CGRP-induced dilation of cerebral arteries [23] also involves $K_V7.4$. However, isoproterenol-dependent activation of $K_V7.4$ involves G-protein $\beta\gamma$ subunits in renal arteries [175]. Data from A7R5 cells suggest that cAMP-PKA targets primarily channels containing $K_V7.5$ [133].

NO-cGMP-PKG-mediated activation of K_V channels

Vasodilators that act through the NO and cGMP signaling pathways also have been suggested to activate K_V channels [184]. Vasodilation induced by endothelium-derived NO, NO-donors and cGMP analogs are inhibited by 4-AP in rat basilar arteries [171]. Nitric oxide and atrial natriuretic peptide activate $K_V2.1$ channels in A7R5 cells and relaxation of rat aortas by these dilators can be inhibited by 4-AP [179]. Coreolide inhibits dilation of the canine coronary circulation to an NO donor suggesting a role for K_V1 channels [49]. Currents through K_V7 channels are also activated by NO and cGMP in rat renal and aortic VSMCs [174]. However, there may be species differences as SNP-induced relaxation of porcine coronary arteries is unaffected by K_V7 channel blockade [79].

Other dilators that activate K_V channels

Hydrogen sulfide (H_2S) [27,134,166] and hydrogen peroxide (H_2O_2) [157,162,163] also act, in part, by activation of VSMC K_V channels. For H_2S, both 4-AP-sensitive K_V channels [27] and K_V7 channels are the targets [134,166]. Hydrogen peroxide activates VSMC 4-AP-sensitive K_V channels through a process that involves thiol oxidation [157,162,163]. In rat mesenteric arteries, S-glutathionylation of $K_V2.1$ has been proposed to underlie the effects of H_2O_2 [157]. In murine coronary arteries, vasodilation induced by H_2O_2 requires expression of VSMC $K_V1.5$ channels [151]. In human coronary arteries, $K_V1.5$ also is the target for H_2O_2-mediated vasodilation [149].

Hypoxia and acidosis may also activate VSMC K_V channels. Hypoxia activates currents through K_V7 channels in SMCs from porcine coronary arteries and mediates hypoxia-

induced relaxation [79]. Acidosis activates 4-AP-sensitive K_V channels in coronary VSMCs [15].

Perivascular adipose tissue (PVAT) release anti-contractile substances (adipocyte-derived relaxing factors - ADRFs) that activate K_V7 channels [180]. In rat gracilis resistance artery VSMCs, ADRFs activate $K_V7.4$ [197].

Functional vasodilation and K_V channels

Blood flow in most tissues is proportional to the tissue's metabolic activity, with increases in metabolism being mirrored by increases in blood flow (functional vasodilation, or functional hyperemia) [47]. Vascular K_V channels have been postulated to mediate functional vasodilation in the heart based on the effects of blockers like 4-AP [16,164] and coreolide [65], for example. However, these studies are difficult to interpret, because the site of action of the K_V channels affected by the drugs (VSMCs, cardiac myocytes, nerves, etc.) is not known. In murine hearts, VSMC-specific knockout of $K_V1.5$ inhibits functional vasodilation, an effect that can be rescued by VSMC expression of $K_V1.5$ [151]. These data support a major role for VSMC $K_V1.5$ in matching blood flow to metabolism in mouse hearts. A role for $K_V1.3$ in coronary functional hyperemia in the mouse also has been proposed [152]. However, because a global $K_V1.3$ knockout was used, the location of the $K_V1.3$ in the signaling pathway that couples cardiac metabolism to blood flow was not established.

K_V channels and pathophysiology

The role played by K_V channels in hypertension [38,46,100,114], obesity and the metabolic syndrome [16,50,97,113,148,194] and aging [62,103] remains unclear. In hypertension, for example, patch-clamp studies have reported increased [40,43], decreased [18,19,37,44,123,135,182] or no change [124,125] in K_V current density. Similarly, expression of K_V channel subunits has been reported to be increased [40,43], decreased [8,9,18,24,95,121,145,182,197,199], or unchanged [9,43,145,197] in SMCs from some vessels in various models of hypertension. Regional differences in the impact of hypertension on K_V channel expression and function; differences in the K_V isoform studied; differences in the model of hypertension used; and differences in the severity and duration of hypertension may explain the lack of consensus reported in the literature.

Voltage-gated K^+ channel expression and function are decreased in experimental models of Type 1 diabetes [21,25,26,114,120,126,159]. Mechanisms involving nitration of K_V channels [120], reactive oxygen species [21], and/or PKC [159] account for the down regulation of K_V channel function in Type 1 diabetes.

Subarachnoid hemorrhage leads to down regulation of K_V channel function in several models of this disease [6,84,91]. In a rabbit model of subarachnoid hemorrhage, oxyhemoglobin-induced activation of tyrosine kinases leads to endocytosis of $K_V1.5$ channels and reduced K_V function [84].

Conclusions and Perspective

Voltage-gated K^+ channels are highly expressed in VSMCs and clearly contribute to the negative feedback regulation of myogenic and agonist-induced tone in resistance arteries and arterioles. What remains unclear is why there are so many isoforms expressed: is this a matter of redundancy or do the different K_V channel isoforms play specific roles that we have yet to unravel? Study of the role played by different K_V isoforms in VSMCs is complex, because there is substantial regional and species differences in channel expression, function and regulation. Thus, information from vessels in one tissue or organ cannot be extrapolated to vessels elsewhere in the body. Our understanding of the composition, complexity and function of protein-protein interactions among K_V channels, signaling proteins and the cytoskeleton is only just beginning and should prove to be fertile ground for future studies. Functions of K_V channel proteins, other than conductance of K^+ flux across biological membrane, as demonstrated by $K_V1.3$ and its role in VSMC proliferation, also remains largely unexplored. Finally, the effects of disease states on the expression and function of K_V channels remains cloudy and poorly understood, particularly with regard to the signaling mechanisms involved. Future studies addressing these issues, particularly in arteriolar smooth muscle from tissues and organs around the body are welcomed.

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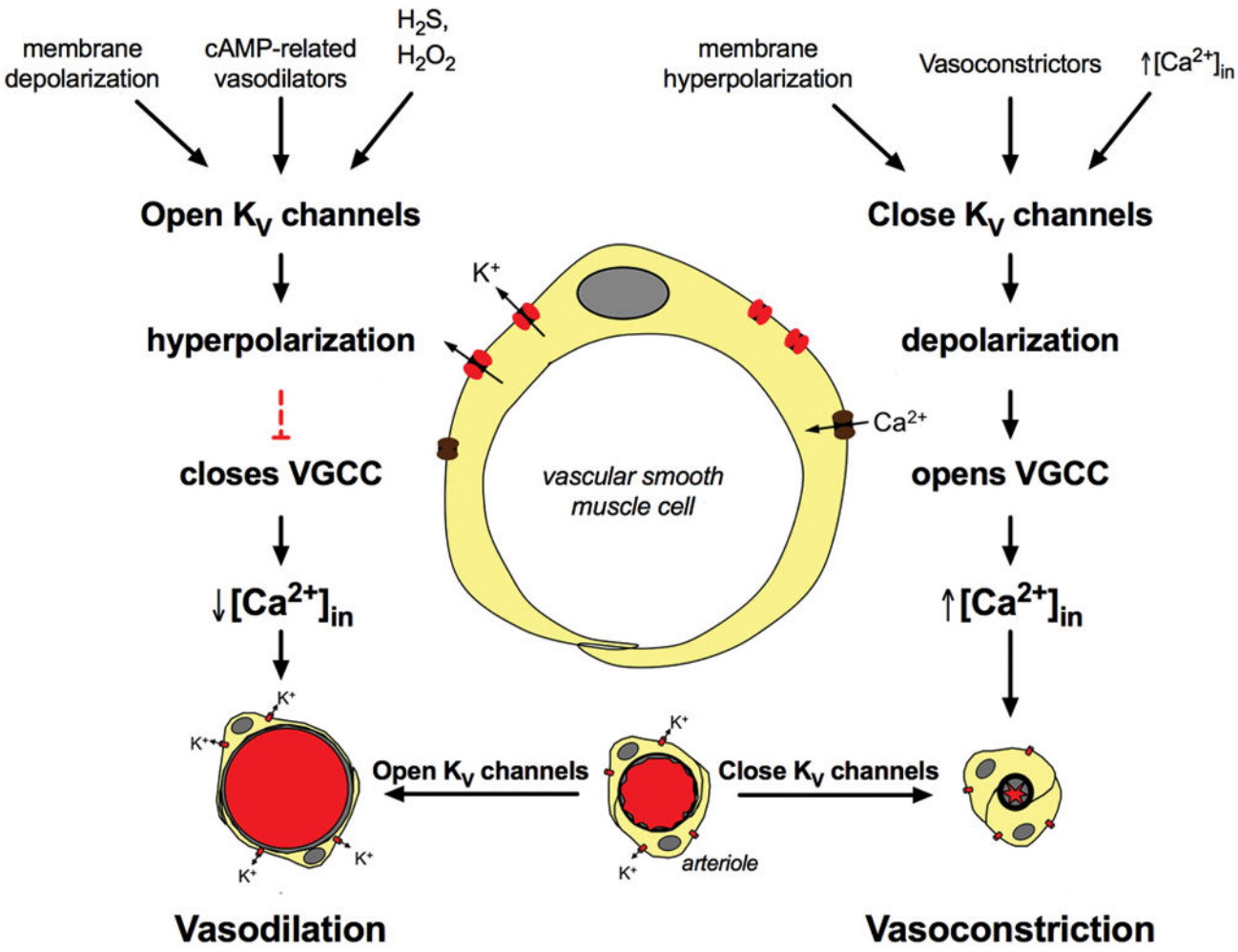

Figure 1.

K_V channels and the regulation of arteriolar tone. Left side of the diagram shows several factors that activate K_V channels in VSMCs (see text for more information and references) leading to K^+ -efflux through these channels, membrane hyperpolarization and ultimately, vasodilation. Right side of diagram shows factors that inhibit K_V channel activity (see text for details and references), leading to membrane depolarization and vasoconstriction.

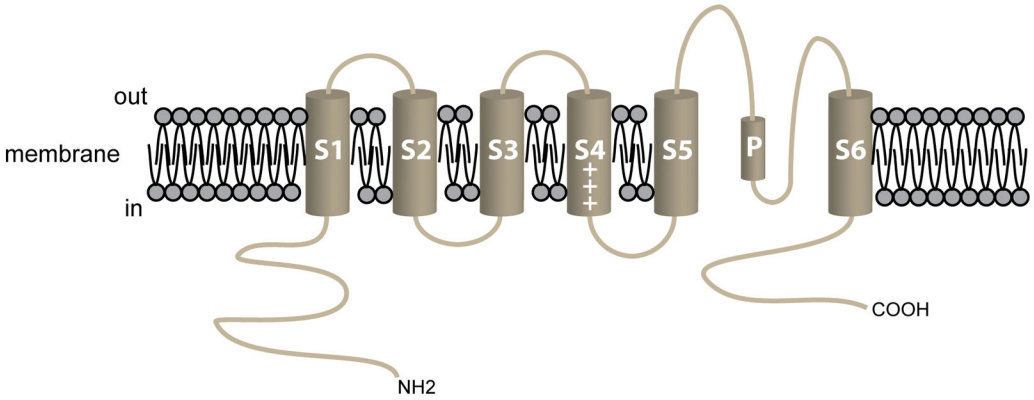

Figure 2.

The pore-forming α-subunit of K_V channels. Schematic diagram of the 6 membrane spanning domains of a typical K_V channel. The length and composition of the amino (NH_2) and the carboxy (COOH) termini vary among the large number of K_V channel isoforms expressed in VSMCs. For K_V1.5, the NH_2-terminus in the full-length version of the channel is 247 amino acids (AAs) and the COOH-terminus is 89 AAs in length. In K_V1.5, the selectivity filter (AAs 480–485) follows the 9 AA, pore helix (AAs 468–479), labeled “P” in the diagram. Modulatory K_Vβ-subunits interact with residues in the NH_2-terminus of the α-subunit. Post-synaptic density (PSD)-95 interacts with PDZ domains in the COOH-terminus of K_V channels.

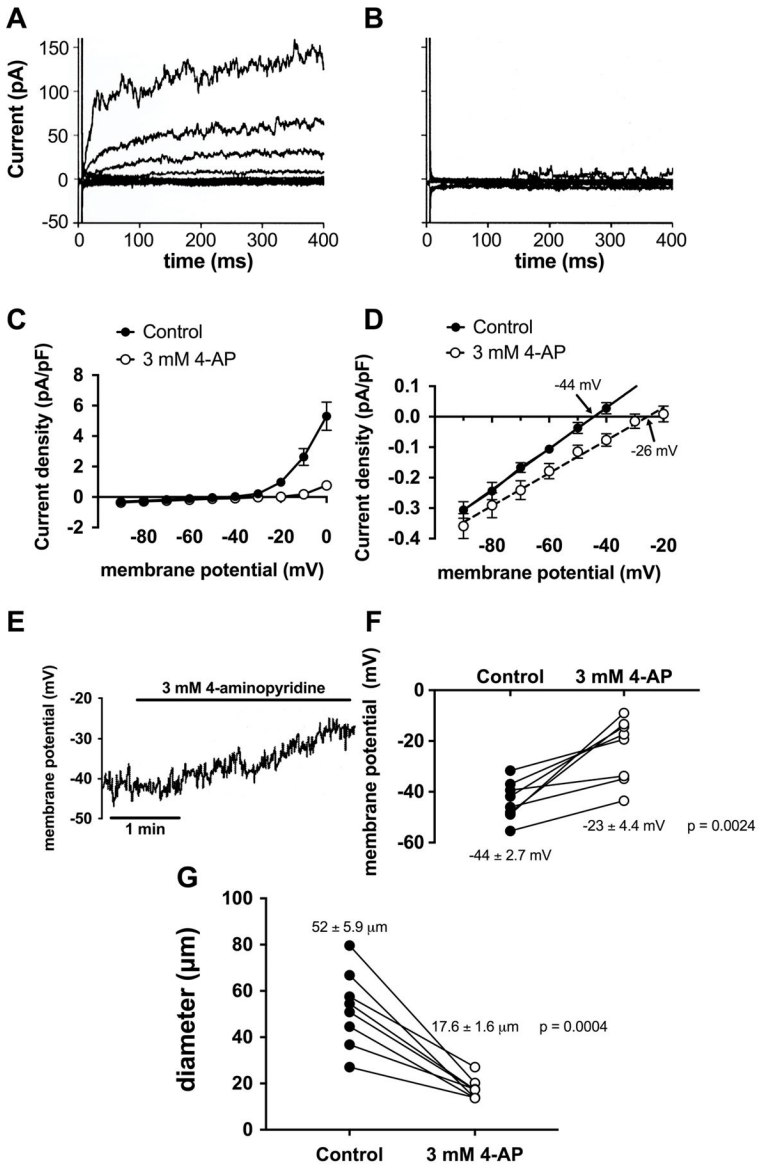

Figure 3.

K_V channel block with 4-aminopyridine inhibits membrane K^+ currents, depolarizes VSMCs and constricts arterioles. Panel A shows the family of outward K^+ currents elicited by 10 mV depolarizing voltage steps from −90 mV to 0 mV recorded in hamster cremasteric arteriolar VSMCs using the perforated patch technique [90]. Panel B shows currents in the same cell after superfusion with 3 mM 4-aminopyridine (4-AP): outward currents are virtually abolished. Panel C shows summary means ± SEM for similar experiments showing the current-voltage relationship for the data shown in Panels A and B. Panel D shows the current-voltage relationship from Panel C on an expanded scale to show that 4-AP (3 mM) inhibits currents around the resting membrane potential of these cells (~-44 mV), and shifts the reversal potential for whole-cell currents (a measure of membrane potential) to more positive potentials. Panel E shows effects of 4-AP (3 mM) on membrane potential of an isolated hamster cremasteric arteriolar VSMC recorded in current-clamp experiments using

the perforated-patch technique: 4-AP depolarized the cell from ~-40 mV to ~-25 mV, consistent with the data shown in Panel D. Panel F shows summary data for experiments as in Panel E demonstrating that 4-AP (3 mM) consistently depolarizes hamster cremasteric arteriolar VSMCs. Panel G shows data from pressure-myography experiments demonstrating that 4-AP consistently constricts isolated second-order cremasteric arterioles, consistent with VSMC depolarization (Panels D–F) due to block of outward K_V currents (Panels A–C). These data show 4-AP-sensitive K_V channel currents contribute to resting membrane potential and myogenic tone in arteriolar VSMCs. Data Panels A–D modified from [90], with permission. Data in Panels E–G replotted from [88], with permission.

Table 1

The pharmacology of VSMC K_V channels

Channel	Gene	Accessory Subunits	Inhibitors/Antagonists (IC_{50})	Activators/Agonists (EC_{50})
K_V1.1	KCNA1	K_V β1, K_V β2	TEA (0.3 mM) [67] 4-AP (0.29 mM) [67] correolide (430 nM) [55] α-dendrotoxin (20 nM) [67] dendrotoxin-k (2.5 nM) [161] hongotoxin (31 pM) [115] margatoxin (144 pM) [115] kaliotoxin (41 nM) [67] ShK toxin (16 pM) [101] Psora-4 (62 nM) [187] PAP-1 (65 nM) [167]	
K_V1.2	KCNA2	K_V β1, K_V β2	TEA (0.56 μM) [67] 4-AP (0.59 mM) [67] correolide (700 nM) [55] charybdotoxin (14 nM) [67] α-dendrotoxin (17 nM) [67] hongotoxin (170 pM) [115] margatoxin (675 pM) [115] ShK toxin (9 nM) [101] Psora-4 (49 nM) [187] PAP-1 (250 nM) [167]	
K_V1.3	KCNA3	K_V β2	TEA (10 mM) [67] 4-AP (0.195 mM) [67] correolide (86 nM) [55] α-dendrotoxin (250 nM) [67] dendrotoxin-k (2.5 nM) [161] hongotoxin (86 pM) [115] margatoxin (230 pM) [115] kaliotoxin (0.65 nM) [67] ShK toxin (11 pM) [101] Psora-4 (3 nM) [187] PAP-1 (2 nM) [167]	
K_V1.5	KCNA5	K_V β1.2, K_V β2, K_V β3	TEA (330 mM) [67] 4-AP (0.27 mM) [67] correolide (1.1 μM) [55] Psora-4 (7.7 nM) [187] PAP-1 (45 nM) [167]	
K_V1.6	KCNA6	K_V β1, K_V β2	TEA (1.7–7 mM) [63,68,109] 4-AP (0.3 – 1.5 mM) [68,109] correolide (450 nM) [55] charybdotoxin (1 nM) [68] α-dendrotoxin (25 nM) [109] hongotoxin (6 nM) [115] margatoxin (144 pM) [115] ShK toxin (165 pM) [101] PAP-1 (62 nM) [167]	
K_V2.1	KCNB1	K_V9.3, K_V6.3	TEA (4.9 mM) [75] 4-AP (18 mM) [110] Ba^{2+} (30 mM) [177] SsmTx-1 (41.7 nM) [28] stromotoxin-1 (12.7 nM) [54] PAP-1 (3 μM) [167]	
K_V3.1	KCNC1		TEA (0.2 mM) [67] 4-AP (29 μM) [67] PAP-1 (5 μM) [167]	
K_V4.1	KCND1		TEA (11 mM) [173] 4-AP (1 mM) [173] phrixotoxin 1 (>250 nM) [51] phrixotoxin 2 (>300 nM) [51]	
K_V4.2	KCND2		TEA (11 mM) [173] 4-AP (1 mM) [173]	

Channel	Gene	Accessory Subunits	Inhibitors/Antagonists (IC_{50})	Activators/Agonists (EC_{50})
			phrixotoxin 1 (5 nM) [51] phrixotoxin 2 (34 nM) [51] PAP-1 (1.2 μM) [167]	
K_V4.3	KCND3		TEA (~11 mM) [173] 4-AP (1.2 mM) [178] phrixotoxin 1 (28 nM) [51] phrixotoxin 2 (71 nM) [51]	
K_V6.3	KCNG3	K_V2.1	See K_V2.1 above	
K_V7.4	KCNQ4	KCNE1–5	TEA (3 mM) [160] Linopirdine (14 μM) [172] XE991 (5.5 μM) [172]	ML277 (>30 μM) [137] ML213 (0.5–0.8 μM) [20,195] Retigabine (5.3 μM) [69]
K_V7.5		KCNE1–5	XE991 (65 μM) [160]	Retigabine (6.4 μM) [69] ML213 (700 nM) [20]
K_V9.3	KCNS3	K_V2.1	See K_V2.1 above	
K_V11.1	KCNH2	KCNE1 (minK)KCNE2 (miRP1)	E4031 (7.7 nM) [202] Dofetilide (6.4 nM) [170] Astemizole (1 nM) [203]	RPR260243 (2 μM) [102] ICA-105574 (0.5 μM) [61] PD-118057 (20 μM) [201] Mallotoxin (0.5 μM) [198] NS1643 (10.5 μM) [72]

Table modified from [184], with permission.