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Potassium Channels in Regulation of Vascular Smooth Muscle Contraction and Growth

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Abstract

Potassium channels importantly contribute to the regulation of vascular smooth muscle (VSM) contraction and growth. They are the dominant ion conductance of the VSM cell membrane and importantly determine and regulate membrane potential. Membrane potential, in turn, regulates the open-state probability of voltage-gated Ca^{2+} channels (VGCC), Ca^{2+} influx through VGCC, intracellular Ca^{2+} and VSM contraction. Membrane potential also affects release of Ca^{2+} from internal stores and the Ca^{2+} sensitivity of the contractile machinery such that K^+ channels participate in all aspects of regulation of VSM contraction. Potassium channels also regulate proliferation of VSM cells through membrane potential-dependent and membrane potential-independent mechanisms. Vascular smooth muscle cells express multiple isoforms of at least five classes of K^+ channels contribute to the regulation of contraction and cell proliferation (growth). This review will examine the structure, expression and function of large-conductance, Ca^{2+}-activated K^+ (BK_{Ca}) channels, intermediate-conductance Ca^{2+}-activated K^+ ($K_{Ca}3.1$) channels, multiple isoforms of voltage-gated K^+ (K_V) channels, ATP-sensitive K^+ (K_{ATP}) channels, and inward-rectifier K^+ (K_{IR}) channels in both contractile and proliferating VSM cells.

Keywords

Potassium channels; vascular smooth muscle; membrane potential; vasoconstriction; vasodilation; proliferation; phenotypic modulation

Introduction

Potassium channels importantly contribute to the regulation of vascular smooth muscle (VSM) contraction and growth. They are the dominant ion conductance of the VSM cell membrane and importantly determine and regulate VSM cell membrane potential (Jackson, 2000, 2005). Membrane potential, in turn, regulates the open-state probability of voltage-gated Ca^{2+} channels (VGCC), Ca^{2+} influx through these channels, intracellular Ca^{2+} and VSM contraction (Jackson, 2000, 2005). Membrane potential also affects release of Ca^{2+} from internal stores and the Ca^{2+} sensitivity of the contractile machinery such that K^+ channels participate in all aspects of regulation of VSM contraction (del Valle-Rodriguez,

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Conflict of Interest Statement:

The author has no conflicts of interest to declare.

Lopez-Barneo, & Urena, 2003; Fernández-Tenorio et al., 2010; Fernandez-Tenorio et al., 2011; V. Y. Ganitkevich & Isenberg, 1993; Kukuljan, Rojas, Catt, & Stojilkovic, 1994; Q. H. Liu et al., 2009; Mahaut-Smith, Martinez-Pinna, & Gurung, 2008; Okada, Yanagisawa, & Taira, 1993; Urena, del Valle-Rodriguez, & Lopez-Barneo, 2007; Yamagishi, Yanagisawa, & Taira, 1992; Yamamura, Ohya, Muraki, & Imaizumi, 2012; Yanagisawa, Yamagishi, & Okada, 1993). Potassium channels also contribute to the regulation of proliferation of VSM cells through membrane potential-dependent (Bi et al., 2013; Miguel-Velado et al., 2005; Miguel-Velado et al., 2010) and membrane potential-independent mechanisms (Cidad et al., 2012; Cidad et al., 2015; Jimenez-Perez et al., 2016).

Vascular smooth muscle cells express multiple isoforms of at least five classes of K^+ channels that participate in the regulation of contraction and cell proliferation (growth). These include large-conductance, Ca^{2+}-activated K^+ (BK_{Ca}) channels, intermediate-conductance Ca^{2+}-activated K^+ ($K_{Ca}3.1$) channels, multiple isoforms of voltage-gated K^+ (K_V) channels, ATP-sensitive K^+ (K_{ATP}) channels, inward-rectifier K^+ (K_{IR}) channels, and members of the two-pore K^+ (K_{2P}) channel family of K^+ channels. Subsequent sections of this review will examine the function of K^+ channels in the regulation of VSM cell contraction and proliferation. The expression and function of K_{2P} channels in VSM cells will not be addressed and the reader is referred to the literature for information on these channels (Feliciangeli, Chatelain, Bichet, & Lesage, 2015; Gurney & Manoury, 2009; O'Connell, Morton, & Hunter, 2002; Renigunta, Schlichthorl, & Daut, 2015; Sepulveda, Pablo Cid, Teulon, & Niemeyer, 2015).

Potassium channels and regulation of VSM contraction

Setting the stage

VSM cells, in small arteries and arterioles that develop myogenic tone when pressurized, are relatively depolarized, with membrane potentials on the order of −45 to −30 mV (Burns, Cohen, & Jackson, 2004; Emerson & Segal, 2000; Knot & Nelson, 1998; Siegl, Koeppen, Wolfle, Pohl, & de Wit, 2005; Welsh, Jackson, & Segal, 1998). At physiological ion concentrations (3–5 mM K^+ extracellular, 140 mM K^+ intracellular), the electrochemical gradient for K^+ (the driving force for movement of K^+ through a K^+ channel) is outward. This means that opening of K^+ channels will lead to K^+ diffusion out of the cell, loss of positive charge and membrane hyperpolarization (M. T. Nelson, Patlak, Worley, & Standen, 1990). Conversely, closure of open K^+ channels will result in a decrease in this hyperpolarizing current, and membrane depolarization. The resistance of the plasma membrane of VSM cells to current flow is very high, on the order of 1–10 GΩ (M. T. Nelson, Patlak, et al., 1990). This means that very small currents produced by only a few active K^+ channels can have very large effects on membrane potential (M. T. Nelson, Patlak, et al., 1990). Voltage-gated Ca^{2+} channels contribute substantially to the regulation of intracellular Ca^{2+} and contraction of VSM cells in differentiated, contractile VSM cells, particularly in resistance arteries and arterioles (M. T. Nelson, Patlak, et al., 1990). Voltage-dependent activation (depolarization) and deactivation (hyperpolarization) of these channels importantly regulates VSM contraction (M. T. Nelson, Patlak, et al., 1990).

The structure of the ion-conducting pore of K^+ channels is thought to be similar across all of the channels based on studies of KcsA, a two transmembrane (TM) domain K^+ channel from *Streptomyces lividans* (Kuang, Purhonen, & Hebert, 2015) (Figure 2). As shown in Figures 2B and 2C, the pore is formed by TM2 and the P-loop, which connects TM1 and TM2. Conserved residues in the P-loop (Thr-Val-Gly-Tyr-Gly) comprise the K^+ selectivity filter (red highlighted segment of the P-loop in Figure 2B) (Kuang et al., 2015). In BK_{Ca} channels and K_V channels, segment 6 (S6) and the P-loop between S5 and S6 form the channels' pores (Figures 3 and 4) (Kuang et al., 2015).

BK_{Ca} channels and VSM contraction

Vascular smooth muscle cells typically express a high density of BK_{Ca} channels in their plasma membranes that importantly contribute to the negative-feedback regulation of vascular tone (Figure 3). A homo-tetramer of α-subunits encoded by the KCNMA1 gene composes the channels (Butler, Tsunoda, McCobb, Wei, & Salkoff, 1993; Pallanck & Ganetzky, 1994) (Figure 3A). Segment 6 and the P-loop connecting S5 and S6 form the ion-conducting pore (Meera, Wallner, Song, & Toro, 1997) (Figure 3A). Two regulator of K^+ conductance (RCK) domains (RCK1 and RCK2) in the C-terminus of the α-subunits contain the channel's Ca^{2+} sensors (Hoshi, Pantazis, & Olcese, 2013) (Figure 3A). Positively charged residues in transmembrane domains S2, S3 and S4 serve as the channel's voltage sensors (Hoshi, Pantazis, et al., 2013) (Figure 3A).

Accessory β_1-subunits (locus: KCNMB1) slow gating kinetics, increase the Ca^{2+} sensitivity, and affect the pharmacology of the channels (McManus et al., 1995; Meera, Wallner, Jiang, & Toro, 1996; Tseng-Crank et al., 1996) (Figure 2). Activation of VSM BK_{Ca} channels by 17β-estradiol, lithocholate, dehydroepiandrosterone. dehydrosoyasaponin-I and docosahexaenoic acid (DHA) requires the presence of β_1-subunits (Hoshi, Tian, Xu, Heinemann, & Hou, 2013; Hou, Heinemann, & Hoshi, 2009). These subunits also contribute to dynamic trafficking of α-subunits to plasma membrane (Leo et al., 2014). The degree of coupling between the α-subunits and the β_1-subunits may account for the high Ca^{2+}-setpoint observed in arteriolar BK_{Ca} channels (Yang et al., 2009; Yang, Sohma, et al., 2013).

In addition to the β_1-subunits, leucine-rich-repeat-containing proteins (LRRCs), such as LRRC26, have been proposed as γ-subunits of VSM BK_{Ca} channels (Evanson, Bannister, Leo, & Jaggar, 2014). These subunits interact with BK_{Ca} channels, increasing both their voltage-sensitivity and channel activation by agents such as NS1619 (Evanson et al., 2014).

Membrane depolarization and increases in intracellular Ca^{2+} activate BK_{Ca} channels (Figure 3B). In many resistance arteries and arterioles that develop pressure-induced myogenic tone, ex vivo, BK_{Ca} channels are active and contribute to resting VSM membrane potential. However, the source of Ca^{2+} responsible for BK_{Ca} channel activation may differ dependent on the anatomical origin of the vessel. Calcium released from groups of ryanodine receptors (RyR) in the sub-plasma membrane endoplasmic reticulum, in the form of Ca^{2+} sparks, control the activity of overlying BK_{Ca} channels in many resistance arteries (Brenner et al., 2000; Bychkov, Gollasch, Ried, Luft, & Haller, 1997; Furstenau et al., 2000; Gollasch et al., 2000; Jaggar, Porter, Lederer, & Nelson, 2000; Jaggar, Stevenson, & Nelson, 1998; Jaggar, Wellman, et al., 1998; Knot, Standen, & Nelson, 1998; M.T. Nelson et al., 1995; M. T.

Nelson & Quayle, 1995; Perez, Bonev, & Nelson, 2001; Perez, Bonev, Patlak, & Nelson, 1999; Porter et al., 1998; Wellman et al., 2002; Wellman & Nelson, 2003). In contrast, Ca^{2+} influx through VGCC may activate BK_{Ca} channels in other vessels including hamster and mouse cremaster arterioles (Westcott, Goodwin, Segal, & Jackson, 2012; Westcott & Jackson, 2011), rabbit coronary arteries (Guia, Wan, Courtemanche, & Leblanc, 1999) and mouse mesenteric arteries (Y. Suzuki, Yamamura, Ohya, & Imaizumi, 2013). In striated muscle resistance arteries, both RyR-based Ca^{2+} sparks and VGCC Ca^{2+}-influx contribute to activation of BK_{Ca} channels (Westcott et al., 2012; Westcott & Jackson, 2011) suggesting that both mechanisms may be active in some cells. In cerebral VSM cells, Ca^{2+} influx through T-type, CaV3.2 VGCC stimulates RyR-based Ca^{2+} sparks contributing to the negative feedback regulation of myogenic tone (Harraz et al., 2014; Harraz et al., 2015).

Vasoconstrictors have been reported to both activate (Berczi, Stekiel, Contney, & Rusch, 1992; Brayden & Nelson, 1992; V. Ganitkevich & Isenberg, 1990; Hashemzadeh-Gargari & Rembold, 1992; Jackson & Blair, 1998; M.T. Nelson et al., 1995; M. T. Nelson & Quayle, 1995; Rusch & Liu, 1997; Wakatsuki, Nakaya, & Inoue, 1992) and inhibit (Lange, Gebremedhin, Narayanan, & Harder, 1997; Scornik & Toro, 1992; Toro, Amador, & Stefani, 1990; Wesselman, Schubert, VanBavel, Nilsson, & Mulvany, 1997) BK_{Ca} channels. Activation of BK_{Ca} channels would tend to hyperpolarize VSM cells, deactivate VGCC and limit VSM contraction, essentially preventing vasospasm (Figure 3B). This activation results from both vasoconstrictor-induced depolarization and increases in intracellular Ca^{2+} (Figure 3B). In contrast, inhibition of BK_{Ca} channels would promote depolarization and would enhance VSM contraction, in a positive feedback fashion. Protein kinase C (PKC), which is commonly activated by vasoconstrictors that activate $G_{q/11}$-coupled, heptihelical receptors, may be involved in this process in some blood vessels (Lange et al., 1997; Minami, Fukuzawa, & Nakaya, 1993), and may involve internalization and degradation of BK_{Ca} channels (Leo et al., 2015). Despite the evidence for inhibition of BK_{Ca} channel activity, the dominant effect of vasoconstrictors in most blood vessels is to activate BK_{Ca} channels.

Vasodilators that act through receptors coupled to the guanine nucleotide binding protein, $G\alpha_s$, and formation of cAMP activate BK_{Ca} channels, as part of their mechanism of action (Kume, Graziano, & Kotlikoff, 1992; Kume, Takai, Tokuno, & Tomita, 1989; Sadoshima, Akaike, Kanaide, & Nakamura, 1988). Activation of BK_{Ca} channels may result from a number of mechanisms. Interaction of $G\alpha_s$ with BK_{Ca} channels, independent from cAMP and protein kinase A (PKA), may increase channel activity (Kume et al., 1992; Kume, Hall, Washabau, Takagi, & Kotlikoff, 1994; Scornik, Codina, Birnbaumer, & Toro, 1993). Protein kinase A-dependent phosphorylation of the α-subunits also can activate BK_{Ca} channels (Nara, Dhulipala, Wang, & Kotlikoff, 1998; Tian et al., 2004; Tian et al., 2001). Increased trafficking of the β1-subunits to the plasma membrane may also contribute to the mechanism of action of cAMP-related agonists (Matsumoto, Szasz, Tostes, & Webb, 2012). Vasodilators that act via cAMP and PKA increase BK_{Ca} channel activity by increasing Ca^{2+} spark activity (Porter et al., 1998; Wellman, Santana, Bonev, & Nelson, 2001; Yamaguchi, Kajita, & Madison, 1995). In addition, exchange proteins activated by cAMP (EPACs) participate in cAMP-related activation of BK_{Ca} channels in VSM (Roberts, Kamishima, Barrett-Jolley, Quayle, & Dart, 2013). Thus, cAMP-related vasodilators may activate BK_{Ca} channels by a number of mechanisms.

Endothelium-derived NO, nitrovasodilators that release NO and other vasodilators that act through the cGMP-protein kinase G (PKG) signaling cascade also have been proposed to activate BK_{Ca} channels (Fujino et al., 1991; P. L. Li, Zou, & Campbell, 1997; Robertson, Schubert, Hescheler, & Nelson, 1993; Taniguchi, Furukawa, & Shigekawa, 1993; Williams, Katz, Roy-Contancin, & Reuben, 1988; Winquist et al., 1985; Winquist, Faison, & Nutt, 1984). This may occur through modulation of Ca^{2+} sparks (Jewell, Saundry, Bonev, Tranmer, & Wellman, 2004; Mandala, Heppner, Bonev, & Nelson, 2007; Yuill, McNeish, Kansui, Garland, & Dora, 2010), by phosphorylation of the channels by PKG (Alioua, Huggins, & Rousseau, 1995; Swayze & Braun, 2001) or altered channel trafficking (Leo et al., 2014). Activation of BK_{Ca} channels by NO, independent from cGMP has also been proposed (Ahern, Hsu, & Jackson, 1999; Bolotina, Najibi, Palacino, Pagano, & Cohen, 1994; Buxton, Kaiser, Malmquist, & Tichenor, 2001; Lang, Harvey, McPhee, & Klemm, 2000; Lang, Harvey, & Mulholland, 2003; P. L. Li, Jin, & Campbell, 1998; Lovren & Triggle, 2000; Mistry & Garland, 1998; Plane, Hurrell, Jeremy, & Garland, 1996; Plane, Sampson, Smith, & Garland, 2001; Yu, Sun, Maier, Harder, & Roman, 2002; Zhang, Tazzeo, Chu, & Janssen, 2006). In contrast, there are also a number of studies that have failed to demonstrate participation of BK_{Ca} channels in the mechanism of action of NO (Armstead, 1997; Bialecki & Stinson-Fisher, 1995; Brayden, 1990; Cooke, Rossitch, Andon, Loscalzo, & Dzau, 1991; H. Dong, Waldron, Galipeau, Cole, & Triggle, 1997; Fukami et al., 1998; Garland & McPherson, 1992; Ghisdal, Gomez, & Morel, 2000; Hansen & Olesen, 1997; Hernanz et al., 1999; Kilpatrick & Cocks, 1994; Plane & Garland, 1993; Plane, Wiley, Jeremy, Cohen, & Garland, 1998; Taguchi, Heistad, Kitazono, & Faraci, 1995; Wellman & Bevan, 1995; Zhu, Beny, Flammer, Luscher, & Haefliger, 1997). Thus, there may be regional or species differences that account for the presence or lack of effect of NO on BK_{Ca} channel activity.

Carbon monoxide (Abraham & Kappas, 2008; Jaggar et al., 2002; Jaggar et al., 2005; A. Li et al., 2008; R. Wang, Wang, & Wu, 1997; R. Wang & Wu, 1997; R. Wang, Wu, & Wang, 1997; Xi et al., 2004; Xi et al., 2010), epoxyeicosatrienoic acids (EETs) (Campbell, Gebremedhin, Pratt, & Harder, 1996; Earley, Heppner, Nelson, & Brayden, 2005; Eckman, Hopkins, McBride, & Keef, 1998), H_2O_2 (Barlow & White, 1998) (Cheranov & Jaggar, 2006; Thengchaisri & Kuo, 2003), and H_2S (Jackson-Weaver et al., 2013; Liang, Xi, Leffler, & Jaggar, 2012) all may activate BK_{Ca} channels. Effects of CO on BK_{Ca} channels may be direct via associated heme proteins that interact with the C-terminal domain of the α-subunits, between RCK1 and RCK2 (Jaggar et al., 2005) or by interaction with histidine residues in RCK1 (Hou et al., 2009) (Figure 3A). In addition, CO augments Ca^{2+} spark frequency and their coupling to BK_{Ca} channels (Jaggar et al., 2002; A. Li et al., 2008; Xi et al., 2010). Epoxyeicosatrienoic acids also may stimulate Ca^{2+} sparks to activate BK_{Ca} channels through actions of EETs on transient receptor potential (TRP) V4 channels (Earley et al., 2005). Stimulation of Ca^{2+} sparks also may underlie the activation of BK_{Ca} channels by H_2S (Jackson-Weaver et al., 2013; Liang et al., 2012).

Diseases and VSM BK_{Ca} channels

The effects of disease states on BK_{Ca} channel expression and function is complex. The activity of BK_{Ca} channels appears to be depressed in obesity (Borbouse et al., 2009;

Borbouse et al., 2010; Frisbee, Maier, & Stepp, 2002; Nystoriak et al., 2014; Ozkor et al., 2011; Rusch, 2009), diabetes (L. Dong et al., 2009; Fernandez-Velasco, Ruiz-Hurtado, Gomez, & Rueda, 2014; Y. Liu & Gutterman, 2002; McGahon et al., 2007; Mokelke, Dietz, Eckman, Nelson, & Sturek, 2005; Nystoriak et al., 2014; Y. Wang et al., 2010; Yi et al., 2014; W. Zhou, Wang, Lamping, & Lee, 2006) and some models of aging (Albarwani, Al-Siyabi, Baomar, & Hassan, 2010; Marijic et al., 2001). In diabetes, the impaired function of BK_{Ca} channels involves reduced expression and function of the β_1-subunits (McGahon et al., 2007; Nystoriak et al., 2014; Yi et al., 2014). Diabetes and hyperglycemia results in increased proteolytic degradation of β_1-subunits via Nuclear Factor (NF)-κB-dependent expression and function of the muscle RING finger protein 1 (MuRF1) ubiquitin ligase (Yi et al., 2014). The down-regulation of the β_1-subunit in diabetes also may involve activation of calcineurin/nuclear factor of activated T-cells, cytoplasmic 3 (NFATC3) signaling that is facilitated by A-kinase anchoring protein 150 (AKAP150) (Nystoriak et al., 2014).

However, the effects of hypertension on BK_{Ca} channel function are not clear, because both increased (Asano, Masuzawa-Ito, & Matsuda, 1993; Asano, Matsuda, Hayakawa, Ito, & Ito, 1993; Y. Liu, Pleyte, Knaus, & Rusch, 1997; Paterno, Heistad, & Faraci, 1997; Rusch, Delucena, Wooldridge, England, & Cowley, 1992; Rusch & Liu, 1997; Zhang, Gao, Zuo, Lee, & Janssen, 2005) and reduced (Amberg, Bonev, Rossow, Nelson, & Santana, 2003; Amberg & Santana, 2003; Ambroisine et al., 2007; Bratz, Dick, Partridge, & Kanagy, 2005; Bratz, Swafford, Kanagy, & Dick, 2005; Callera, Yogi, Tostes, Rossoni, & Bendhack, 2004; Z. Li, Lu, & Shi, 2014; Moreno-Dominguez, Cidad, Miguel-Velado, Lopez-Lopez, & Perez-Garcia, 2009; Nieves-Cintron, Amberg, Nichols, Molkentin, & Santana, 2007; Yang, Li, et al., 2013) function has been reported. Differences in hypertension models, duration of hypertension, type of blood vessel and the species studied may account for the lack of consensus on the effects of hypertension on BK_{Ca} channel function.

K_V channels and VSM contraction

Vascular smooth muscle cells express a diverse array of K_V channels that include members of the K_V1 (loci: KCNA2-6)(Cox, 2005), K_V2 (loci: KCNB2-3) (Cox, 2005), K_V3 (loci: KCNC2-4)(Cox, 2005), K_V4 (loci: KCND1-3) (Cox, 2005), $K_V6.3$ (locus: KCNG3) (Moreno-Dominguez et al., 2009), K_V7 (loci:KCNQ1, KCNQ4-5) (Greenwood & Ohya, 2009; Jepps, Olesen, & Greenwood, 2013; Mackie & Byron, 2008) and $K_V9.3$ (locus: KCNS3) (Cox, 2005) families of K_V channels. They consist of homo- or heterotetramers of α-subunits (Figure 4) (Kuang et al., 2015). Segment 6 (S6) and the P-loop between S5 and S6 forms the channel's pore, as noted above (Kuang et al., 2015). Positively charged residues in S4 confer voltage sensitivity to the channels (Figure 4) (Kuang et al., 2015). Modulatory accessory subunits accompany many K_V channels, affecting channel membrane expression, gating kinetics, and voltage sensitivity (Gutman et al., 2005).

Membrane depolarization activates K_V channels, and, in general, they participate in the negative feedback regulation of VSM contraction along with BK_{Ca} channels. Consistent with this negative-feedback role, block of K_V channels potentiates VSM contraction induced by vasoconstrictors (Chadha et al., 2014; Cheong, Dedman, & Beech, 2001; Cheong, Dedman, Xu, & Beech, 2001; Cook, 1989; Hald et al., 2012; Martinez et al., 2009; Pagan et

al., 2009; Shimizu, Yokoshiki, Sperelakis, & Paul, 2000). Voltage-gated K^+ channels are active at the resting membrane potential of VSM cells in blood vessels displaying myogenic tone; closure of these channels leads to membrane depolarization and vasoconstriction (Cox, 2005; Jackson, 2000, 2005; M. T. Nelson & Quayle, 1995).

Vasoconstrictors, including phenylephrine (Mistry & Garland, 1999), 5-HT (Bae et al., 2006; Ko, Park, Firth, Hong, et al., 2010; Sung et al., 2013) and angiotensin II (Clement-Chomienne, Walsh, & Cole, 1996) all inhibit K_V channels, probably acting through PKC (Clement-Chomienne et al., 1996; Hayabuchi, Standen, & Davies, 2001; Ko, Park, Firth, Hong, et al., 2010), Src tyrosine kinase (Sung et al., 2013), Rho kinase (Luykenaar, Brett, Wu, Wiehler, & Welsh, 2004; Luykenaar, El-Rahman, Walsh, & Welsh, 2009) and/or increased intracellular Ca^+ (Cox & Petrou, 1999; Gelband, Ishikawa, Post, Keef, & Hume, 1993; Ishikawa, Hume, & Keef, 1993). This closure of K_V channels may contribute to vasoconstrictor-induced VSM cell membrane depolarization and the mechanism of action of vasoconstrictors.

Vasodilators acting through the cAMP-PKA pathway activate K_V channels and contribute to their mechanism of action (E. A. Aiello, Malcolm, Walsh, & Cole, 1998; E.A. Aiello, Walsh, & Cole, 1994; E. A. Aiello, Walsh, & Cole, 1995; Berwick et al., 2010; Chadha et al., 2014; Chadha et al., 2012; Dick et al., 2008; H. Dong, Waldron, Cole, & Triggle, 1998; Heaps & Bowles, 2002; Heaps, Tharp, & Bowles, 2005; Khanamiri et al., 2013; H. Li, Chai, Gutterman, & Liu, 2003; Moore, Nelson, Parelkar, Rusch, & Rhee, 2014; Satake, Shibata, & Shibata, 1996). Nitric oxide (Dick et al., 2008; Sobey & Faraci, 1999; Stott, Barrese, Jepps, Leighton, & Greenwood, 2015; Tanaka et al., 2006), H_2S (Cheang et al., 2010; Martelli et al., 2013; Rogers, Chilian, Bratz, Bryan, & Dick, 2007; Schleifenbaum et al., 2010), hypoxia (Hedegaard et al., 2014), acidosis (Berger, Vandier, Bonnet, Jackson, & Rusch, 1998) and anticontractile substances release by perivascular adipose tissue (Tano, Schleifenbaum, & Gollasch, 2014; Zavaritskaya et al., 2013) also may activate VSM K_V channels in some blood vessels.

Disease and VSM K_V channels

The expression and function of K_V channels is reduced in diabetes (Bubolz, Li, Wu, & Liu, 2005; Chai, Liu, & Chen, 2005; Chai et al., 2007; Ko, Park, Firth, Kim, et al., 2010; H. Li et al., 2003) that may be mediated by elevated glucose (H. Li, Gutterman, Rusch, Bubolz, & Liu, 2004; Y. Liu, Terata, Rusch, & Gutterman, 2001) and channel nitration (H. Li et al., 2004). The reduced K_V channel function may contribute to the increased VSM contractile function that is observed in diabetes.

However, in hypertension and obesity, the impact on K_V channels is not as clear. Increased (Cox, Folander, & Swanson, 2001; Cox, Fromme, Folander, & Swanson, 2008), decreased (Bratz, Dick, et al., 2005; Bratz, Swafford, et al., 2005; Cox, 1996; Cox, Lozinskaya, & Dietz, 2001; Y. Liu, Hudetz, Knaus, & Rusch, 1998; Martens & Gelband, 1996; Tobin et al., 2009) or no change (Y. Liu, Jones, & Sturek, 1994; Y. Liu et al., 1997) in K_V channel function in hypertension has been reported. There also is no clear effect of obesity on K_V channel function, with decreased (Berwick et al., 2012; Dick & Tune, 2010; Nieves-Cintron et al., 2015; Yang, Jones, Thomas, & Rubin, 2007) and increased (J. Jiang, Thoren,

Caligiuri, Hansson, & Pernow, 1999; Ko, Park, Firth, Hong, et al., 2010) function reported. Specific effects may depend on the vascular bed studied, the duration and severity of the pathology and the species studied.

K_{ATP} Channels and VSM Contraction

Vascular smooth muscle cells express K_{ATP} channels that consist of tetramers of pore-forming $K_{IR}6.1$ subunits (locus: KCNJ8) (Aziz et al., 2014; A. Li et al., 2013; Miki et al., 2002; Miura et al., 2003; M. Suzuki et al., 2001; Yamada et al., 1997), associated with an equal number of accessory sulphonylurea receptors (SUR) 2B (locus: ABCC9) (Adebiyi, McNally, & Jaggar, 2011; Miura et al., 2003; Quayle, Nelson, & Standen, 1997) (Figure 5). These channels were named because millimolar intracellular ATP closes the channels (Foster & Coetzee, 2016). However, their modulation by vasodilator substances is probably more important for their physiological function. Sensitivity to ATP is conferred by the KIR6.1 subunit, whereas sensitivity to channel blockade by sulphonylureas, such as glibenclamide, and activation by agonists such pinacidil and cromakalim resides in the SUR2B subunit (Foster & Coetzee, 2016).

Vascular K_{ATP} channels appear to be active under resting conditions in coronary (Berwick et al., 2010; Dankelman, Van der Ploeg, & Spaan, 1994; Duncker, van Zon, Pavek, Herrlinger, & Bache, 1995; Farouque & Meredith, 2007; Farouque, Worthley, & Meredith, 2004; Farouque, Worthley, Meredith, Skyrme-Jones, & Zhang, 2002; Imamura et al., 1992; Jackson, Konig, Dambacher, & Busse, 1993; Merkus et al., 2003; Merkus, Sorop, Houweling, Hoogteijling, & Duncker, 2006; Mori et al., 1995; Randall, 1995; Richmond, Tune, Gorman, & Feigl, 1999, 2000; Samaha, Heineman, Ince, Fleming, & Balaban, 1992; Sharifi-Sanjani et al., 2013; Stepp, Kroll, & Feigl, 1997; X. Zhou, Teng, Tilley, Ledent, & Mustafa, 2014), skin (Abbink et al., 2002; Cankar & Strucl, 2008; Hojs, Strucl, & Cankar, 2009) and renal (Duncker, Oei, Hu, Stubenitsky, & Verdouw, 2001; Holdsworth et al., 2015) circulations, at rest. The resting activity of KATP channels is not as clear in skeletal muscle, because there is evidence both for (Jackson, 1993; Kosmas, Levy, & Hussain, 1995; Saito, McKay, Eraslan, & Hester, 1996; Vanelli, Chang, Gatensby, & Hussain, 1994; Vanelli & Hussain, 1994) and against (Banitt, Smits, Williams, Ganz, & Creager, 1996; Bank, Sih, Mullen, Osayamwen, & Lee, 2000; Bijlstra et al., 1996; Duncker et al., 2001; Farouque & Meredith, 2003a, 2003b, 2003c; Hammer, Ligon, & Hester, 2001; Holdsworth et al., 2015; Murrant & Sarelius, 2002) resting activity of these channels. In the cerebral circulation, K_{ATP} channels appear to be closed at rest (Faraci & Heistad, 1998; Horinaka et al., 1997; Leffler et al., 2011; Lindauer, Vogt, Schuh-Hofer, Dreier, & Dirnagl, 2003; Nnorom et al., 2014; Toyoda et al., 1997; Wei & Kontos, 1999).

Vasoconstrictors that activate PKC, close VSM K_{ATP} channels (Bonev & Nelson, 1996; Chrissobolis & Sobey, 2002; Cole, Malcolm, Walsh, & Light, 2000; Hayabuchi, Davies, & Standen, 2001; Quinn, Cui, Giblin, Clapp, & Tinker, 2003; Sampson, Davies, Barrett-Jolley, Standen, & Dart, 2007) and cause channel internalization (Jiao, Garg, Yang, Elton, & Hu, 2008). Vasoconstrictor-induced increases in intracellular Ca^{2+} also lead to K_{ATP} channel closure through activation of protein phosphatase 2b (calcineurin) (Wilson, Jabr, & Clapp, 2000). Vasoconstrictor-induced activation of $G_{i/o}$ signaling also inhibits K_{ATP} channels

through inhibition of adenylate cyclase, reduced cAMP and decreased channel phosphorylation (Hayabuchi, Davies, et al., 2001).

As with BK_{Ca} channels and K_V channels, vasodilators that signal through the cAMP signaling pathway activate K_{ATP} channels (Akatsuka et al., 1994; Bouchard, Dumont, & Lamontagne, 1994; Dart & Standen, 1993; Eguchi et al., 2007; Jackson, 1993; Kitazono, Heistad, & Faraci, 1993b; Kleppisch & Nelson, 1995; Ming, Parent, & Lavallee, 1997; Nakashima & Vanhoutte, 1995; C. P. Nelson et al., 2011; M. T. Nelson, Huang, Brayden, Hescheler, & Standen, 1990; Quayle, Bonev, Brayden, & Nelson, 1994; Randall, 1995; Sawmiller, Ashtari, Urueta, Leschinsky, & Henning, 2006; Wellman, Quayle, & Standen, 1998; Yang et al., 2008). This may involve phosphorylation of both $K_{IR}6.1$ (Quinn, Giblin, & Tinker, 2004) and SUR2B (Shi et al., 2008; Shi et al., 2007) subunits. Hydrogen sulfide (Cheng, Ndisang, Tang, Cao, & Wang, 2004; Leffler et al., 2011; Liang et al., 2011; Mustafa et al., 2011; Zhao, Zhang, Lu, & Wang, 2001), acidosis (Faraci, Breese, & Heistad, 1994; Heintz, Damm, Brand, Koch, & Deussen, 2008; Lindauer et al., 2003) and hypoxia (Daut et al., 1990; Loutzenhiser & Parker, 1994; Marshall, Thomas, & Turner, 1993; Nakhostine & Lamontagne, 1993, 1994; Taguchi, Heistad, Kitazono, & Faraci, 1994; Tomiyama, Brian, & Todd, 1999; von Beckerath, Cyrys, Dischner, & Daut, 1991) may act, in part, in some vascular beds, by activation of VSM K_{ATP} channels.

Disease and VSM K_{ATP} channels

The function of VSM K_{ATP} channels appears to be decreased in obesity (Erdos, Miller, & Busija, 2002; Erdos, Simandle, Snipes, Miller, & Busija, 2004; Hodnett, Xiang, Dearman, Carter, & Hester, 2008; Irat, Aslamaci, Karasu, & Ari, 2006; Lu et al., 2013; Miller, Tulbert, Puskar, & Busija, 2002; Spallarossa et al., 2001) and diabetes (Bouchard, Dumont, & Lamontagne, 1999; Kamata, Miyata, & Kasuya, 1989; Kinoshita et al., 2006; S. S. Li et al., 2015; Mayhan, 1994; Mayhan & Faraci, 1993; Miura et al., 2003). However, in hypertension K_{ATP} channel function has been reported to be decreased (Ghosh, Hanna, Wang, & McNeill, 2004; Kalliovalkama et al., 1999; Kam, Pfaffendorf, & van Zwieten, 1994; Kawata et al., 1998; Kitazono, Heistad, & Faraci, 1993a; Ohya et al., 1996; Tajada, Cidad, Moreno-Dominguez, Perez-Garcia, & Lopez-Lopez, 2012; Takaba et al., 1996; Van de Voorde, Vanheel, & Leusen, 1992), increased (Furspan & Webb, 1993; Miyata, Tsuchida, & Otomo, 1990) or not changed (Blanco-Rivero et al., 2008; Hutri-Kahonen et al., 1999; Kolias, Chai, & Webb, 1993).

K_{IR} channels and VSM contraction

Vascular smooth muscle cells, particularly those in small resistance arteries and arterioles, also express one or more members of the strong inward rectifier K^+ channels, with $K_{IR}2.1$ (locus: KCNJ2) being the dominant isoform expressed (Longden & Nelson, 2015). These channels are formed from a tetramer of two-membrane spanning domain K_{IR} channel subunits (Kuang et al., 2015) (Figure 6A). Block of the channel pore by intracellular polyamines and Mg^{2+} is responsible for the strong, voltage-dependent inward current rectification that is characteristic of these channels (Kuang et al., 2015) (Figure 6B).

While these channels derive their name from the inward currents that they conduct at membrane potentials more negative than the K^+ equilibrium potential (E_K), it is the small, outward "hump" in the current-voltage relationship at potentials positive to E_K that contributes to their physiology (Longden & Nelson, 2015; Quayle et al., 1997) (Figure 6B).

Current through K_{IR} channels contributes to the resting membrane potential in a number of vascular beds (Burns et al., 2004; Chilton et al., 2008; Chilton & Loutzenhiser, 2001; Chilton, Smirnov, Loutzenhiser, Wang, & Loutzenhiser, 2011; Edwards & Hirst, 1988; Edwards, Hirst, & Silverberg, 1988; Jantzi et al., 2006; Z. G. Jiang, Si, Lasarev, & Nuttall, 2001; Johnson, Marrelli, Steenberg, Childres, & Bryan, 1998; McCarron & Halpern, 1990; Smith et al., 2008; Troncoso Brindeiro, Fallet, Lane, & Carmines, 2008; Wu et al., 2007). Importantly, because of the shape of the current-voltage relationship, anything that hyperpolarizes the membrane will recruit outward current through K_{IR} channels (See Figure 6B). Thus, these channels act to amplify hyperpolarization induced by opening of other K^+ channels or other cellular processes, such as the Na^+/K^+ ATPase, and thus, may contribute to the mechanism of action of a number of vasodilators (Jackson, 2005; Jantzi et al., 2006; Longden & Nelson, 2015; Smith et al., 2008; Sonkusare, Dalsgaard, Bonev, & Nelson, 2016).

Increases in extracellular K^+ also activate K_{IR} channels, allowing these channels to contribute to functional hyperemia in electrically active tissues such as the brain (Filosa et al., 2006; Girouard et al., 2010; Paisansathan, Xu, Vetri, Hernandez, & Pelligrino, 2010; Vetri, Xu, Paisansathan, & Pelligrino, 2012) and skeletal muscle (Armstrong, Dua, & Murrant, 2007; Crecelius, Kirby, Luckasen, Larson, & Dinenno, 2013; Crecelius, Luckasen, Larson, & Dinenno, 2014) (Figure 6C). These channels may also be activated by K^+ released through other VSM or endothelial cell K^+ channels, another means by which K_{IR} channels can amplify the effects of vasodilators (Busse et al., 2002; Haddy, Vanhoutte, & Feletou, 2006; Longden & Nelson, 2015).

Vasoconstrictors may close K_{IR} channels through mechanisms involving PKC (Henry, Pearson, & Nichols, 1996; Park, Han, Kim, Youm, et al., 2005; Park et al., 2006; Zitron et al., 2004) or tyrosine kinases (Wischmeyer, Doring, & Karschin, 1998; Zitron et al., 2008), although this has not been well studied in blood vessels. Vasodilators that act through cAMP signaling may activate K_{IR} channels in some blood vessels (Paisansathan et al., 2010; Park, Han, Kim, Ko, et al., 2005; Son et al., 2005). However, it is unclear whether this is due to PKA-dependent phosphorylation of K_{IR} channels, or due to activation of other K^+ channels and amplification of hyperpolarization initiated by the opening of the other channel, as noted above.

Diseases and VSM K_{IR} channels

The effects of hypertension on K_{IR} channel function are not clear; increases (Nakahata et al., 2006), decreases (Seo et al., 2014), or no change in function (Tajada et al., 2012) have been reported. Similarly, diabetes has been reported to increase (Troncoso Brindeiro et al., 2008; Troncoso Brindeiro, Lane, & Carmines, 2012) or decrease (Matsushita & Puro, 2006; Mayhan, Mayhan, Sun, & Patel, 2004; Vetri et al., 2012) K_{IR} channel function in different

models. Regional, species or model dependent differences could be responsible for this heterogeneity.

Obesity (de Kreutzenberg et al., 2003; Haddock et al., 2011; Vigili de Kreutzenberg, Kiwanuka, Tiengo, & Avogaro, 2003), stress (Longden, Dabertrand, Hill-Eubanks, Hammack, & Nelson, 2014), and ischemia (Bastide et al., 1999; Bastide et al., 2003; Marrelli, Johnson, Khorovets, Childres, & Bryan, 1998; Povlsen, Longden, Bonev, Hill-Eubanks, & Nelson, 2016) all are associated with decreased K_{IR} channel function. Membrane cholesterol and hypercholesterolemia strongly suppresses K_{IR} channel function in other systems (Fang et al., 2006). However, the effects of hypercholesterolemia on VSM K_{IR} channel expression and function have not been directly studied.

K^+ channels and VSM proliferation

Remodeling of blood vessels after injury or due to diseases, such as atherosclerosis, results in phenotypic modulation of VSM cells from a quiescent, non-dividing, contractile phenotype into proliferating cells. Potassium channels importantly contribute to the proliferative phenotype in VSM cells. An increase in K^+ channel expression and function is required for cells to proliferate (Neylon, 2002; Pardo, 2004; Urrego, Tomczak, Zahed, Stuhmer, & Pardo, 2014; Wonderlin & Strobl, 1996). Inhibition of K^+ channel function attenuates proliferation of VSM (Kohler et al., 2003; Miguel-Velado et al., 2005; Neylon, 2002; Tharp & Bowles, 2009; Tharp, Wamhoff, Turk, & Bowles, 2006) and other cells (Pardo, 2004; Urrego et al., 2014; Wonderlin & Strobl, 1996). Potassium channels are required for cells to progress through the cell cycle, as during proliferation (Urrego et al., 2014). They participate in this process by several mechanisms including membrane potential regulation, cell volume regulation, and ion-permeation-independent mechanisms (Urrego et al., 2014). Potassium channels also participate in apoptosis, a required component of vascular remodeling after injury (Kondratskyi, Kondratska, Skryma, & Prevarskaya, 2015).

In quiescent, contractile VSM cells, Ca^{2+} influx through high-voltage-activated, L-type VGCC importantly contributes to cell Ca^{2+} regulation and contractile function (Jackson, 2000, 2005) (Figures 1 and 3B). In this setting, activation of K^+ channels leads to membrane hyperpolarization, closure of VGCC and decreases in intracellular Ca^{2+} (Jackson, 2000, 2005) (Figures 1 and 3B). These cells also express a number of members of the transient receptor potential (TRP) family of ion channels including TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, TRPM4, and TRPV4 (Earley & Brayden, 2015). These channels serve as store-operated channels (SOC; TRPC1, TRPC4, TRPC5), receptor operated channels (ROC; TRPC3, TRPC6, TRPM4, TRPV4), and stretch-activated channels (SAC; TRPC6, TRPM4) that contribute to agonist and pressure-induced contraction of native VSM cells (Earley & Brayden, 2015). However, in proliferating VSM cells, there is significant ion channel remodeling: expression of L-type VGCC is reduced, whereas expression of T-type VGCC, TRPC1, TRPC6 and SOC composed of ORAI and the endoplasmic reticulum Ca^{2+}-sensing protein, STIM is increased (Beech, 2007; House, Potier, Bisaillon, Singer, & Trebak, 2008; Munoz et al., 2013; Trebak, 2012; Tzeng et al., 2012) (Figure 7). Importantly, there are also changes in K^+ channel expression that are essential for VSM cells to progress through the cell cycle and proliferate (Figure 7, and sections below). During proliferation, increased

expression and activation of a K^+ channel will either hyperpolarize the membrane to increase or maintain the electrochemical gradient for Ca^{2+} entry through TRP channels and ORAI/STIM-based SOC (e.g., Figure 8), which will increase or sustain Ca^{2+} influx through these channels (Bi et al., 2013; Munoz et al., 2013; Urrego et al., 2014). Increased intracellular Ca^{2+} concentration is an important signal for cell proliferation (Bi et al., 2013; Munoz et al., 2013; Urrego et al., 2014). As noted above, other roles for K^+ channels are also possible (Cidad et al., 2012; Cidad et al., 2015; Urrego et al., 2014).

$K_{Ca}3.1$ and VSM proliferation

The intermediate-conductance Ca^{2+}-activated K^+ channel, $K_{Ca}3.1$ (sK4, IK1, locus: *KCNN4*) has consistently been shown to play an important role in proliferation of VSM (Gole, Tharp, & Bowles, 2014; Kohler et al., 2003; Neylon, 2002; Tharp et al., 2006; Toyama et al., 2008) and other cells (Urrego et al., 2014) (Figure 8). These K^+ channels are voltage insensitive and use calmodulin as the Ca^{2+} sensor (Fanger et al., 1999). Calmodulin interacts with the intracellular C-terminus of the channel to gate channel opening (Fanger et al., 1999) (Figure 8A). The concentration of free Ca^{2+} required for 50% of maximal activation of $K_{Ca}3.1$ is on the order of 300 nM, with the threshold for activity at approximately 100 nM and maximal activity at 1 μM (Ishii et al., 1997).

Growth factors upregulate expression of $K_{Ca}3.1$ in cultured VSM cells (Gole et al., 2014; Kohler et al., 2003; Neylon, 2002; Tharp et al., 2006; Toyama et al., 2008). In porcine coronary artery VSM cells, NADPH oxidase 5 (NOX5)-related increases in reactive oxygen species appear to mediate the upregulation of $K_{Ca}3.1$ expression that results from simulation by basic fibroblast growth factor (Gole et al., 2014). Growth factors regulate expression of $K_{Ca}3.1$ both by decreasing the activity of repressor element 1-silencing transcription factor (REST) (Cheong et al., 2005) and by increasing activity of the AP-1 transcription factor (Bi et al., 2013; Ghanshani et al., 2000). Nucleoside diphosphate kinase B-dependent phosphorylation of $K_{Ca}3.1$ may contribute to activation of these channels in a mouse model of vascular injury (X. B. Zhou et al., 2015).

Selective inhibition of $K_{Ca}3.1$ reduces VSM cell growth and proliferation (Kohler et al., 2003; Neylon, 2002; Tharp et al., 2006; Toyama et al., 2008). Importantly, inhibition of these channels lessens restenosis after balloon injury in rat (Kohler et al., 2003) and pig (Tharp et al., 2008), and limits VSM proliferation in a mouse model of atherosclerosis (Toyama et al., 2008). These ion channels also have been implicated in the VSM proliferation that occurs after organ transplantation (Chen, Lam, Gregory, Schrepfer, & Wulff, 2013) and in chronic kidney disease (Huang, Pollock, & Chen, 2015). The pro-proliferative effect of $K_{Ca}3.1$ is mediated by increases in intracellular Ca^{2+} (Bi et al., 2013), likely due to increased influx of extracellular Ca^{2+} driven by $K_{Ca}3.1$-induced hyperpolarization and the increased electrochemical gradient for Ca^{2+} influx through TRP channels and ORAI/STIM-based SOC (Figure 8B). The pro-proliferative effect of increases in intracellular Ca^{2+} involves phosphorylated cAMP-response element-binding protein (CREB), c-Fos, and neuron-derived orphan receptor-1 (NOR-1) in human coronary VSM cells (Bi et al., 2013). Unexpectedly, activators of $K_{ca}3.1$ such as EBIO, SKA-31 and NS309 attenuated platelet-derived-growth-factor (PDGF)-induced proliferation of these cells (Bi et

al., 2013). The inhibition of PDGF-induced proliferation appeared to arise from strong suppression of $K_{Ca}3.1$ expression by the activators, and the resultant reduction in intracellular Ca^{2+} signaling (Bi et al., 2013).

K_V channels and VSM proliferation

In addition to $K_{Ca}3.1$, there are also K_V channels that contribute to VSM cell proliferation. The K_V channel, $K_V3.4$ (locus: *KCNC4*) is upregulated during proliferation of human uterine artery VSM cells, and selective inhibition of $K_V3.4$ blocks proliferation (Miguel-Velado et al., 2005; Miguel-Velado et al., 2010) and prevents progression of the cells through the G1 phase of the cell cycle (Miguel-Velado et al., 2010). The inhibitory effects of Kv3.4 blockade on proliferation could be mimicked by incubation of cells with elevated extracellular K^+ to produce depolarization equivalent to that produced by $K_V3.4$ blockade (Miguel-Velado et al., 2010). These data suggest that the proliferative effects of $K_V3.4$ may be related to the channel's impact on membrane potential (hyperpolarization), similar to the proposed mechanism for $K_{Ca}3.1$ channel stimulation of Ca^{2+} influx (Figure 8B).

In contrast, balloon-injury of mouse arteries results in upregulation of $K_V1.3$ (locus: *KCNE3*) (Cidad et al., 2010) and downregulation of $K_V1.5$ (Cidad et al., 2012; Cidad et al., 2015; Cidad et al., 2014). Proliferation and migration of VSM cells in this model can be attenuated by selective blockade of $K_V1.3$ channels (Cheong et al., 2011; Cidad et al., 2010). Studies in human VSM cells also confirm a role for $K_V1.3$ in proliferation (Cheong et al., 2011; Cidad et al., 2015). Interestingly, $K_V1.3$ may contribute to VSM proliferation by ion-permeation-independent mechanisms (Cidad et al., 2012; Cidad et al., 2015; Jimenez-Perez et al., 2016). The pro-proliferative effects of $K_V1.3$ are mediated by voltage-dependent exposure of key residues in the channel's C-terminus (Tyr-447 and Ser-459) (Jimenez-Perez et al., 2016). These K_V channels may act as scaffolding proteins that recruit signaling proteins into signalplexes to promote the proliferative phenotype, independent from K^+ diffusion through the pore of the channel and changes in membrane potential (Cahalan & Chandy, 2009; Jimenez-Perez et al., 2016; Schwab, Hanley, Fabian, & Stock, 2008). In human coronary VSM cells, this may involve mitogen-activated protein kinase kinase (MEK)/extracellular signal–regulated kinase (ERK) and phospholipase Cγ signaling pathways (Cidad et al., 2015). This may provide additional targets to combat vascular proliferative diseases, in addition to the Phosphatidylinositol-4,5-bisphosphate 3-kinase/ mammalian target of rapamycin (mTOR) pathway targeted by current therapies (Cidad et al., 2015).

Summary and questions for the future

While we have learned much about the expression and function of K^+ channels in the regulation of VSM contraction and proliferation in the past 30 years, there remain several outstanding questions. First, why do VSM cells express so many different K_V channels? Is this simply a matter of redundancy, or does the pattern of expression of these channels tune the electrophysiology of VSM cells in different vascular beds in ways that are not yet clear (Zhong et al., 2010)? Second, while it is clear that K^+ channels, like all ion channels, exist in multi-protein signaling domains (Abriel, Rougier, & Jalife, 2015; Kim & Oh, 2016; Levitan,

2006), our understanding of the regional heterogeneity in the nature and composition of these signaling domains in different vascular beds is incomplete. Finally, our understanding of the regulation of expression and function of K^+ channels in major cardiovascular disease states also remains incomplete, particularly as they relate to different vascular beds around the body. These are research areas where single cell transcriptome studies, high resolution proteomics and informatics along with detailed electrophysiology and mechanical studies would aid in providing a clearer picture of the expression and function of the diverse array of K^+ channels that contribute to the regulation of VSM contraction and proliferation in health and disease.

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Abbreviations

EBIO	1-Ethyl-2-benzimidazolinone
NS1619	1,3-Dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-benzimidazol-2-one
NS309	6,7-Dichloro-1H-indole-2,3-dione 3-oxime
AKAP	A-kinase anchoring protein
NH_2	amino
K_{ATP}	ATP-sensitive K^+
CREB	cAMP-response element-binding protein
CO	Carbon monoxide
COOH	carboxy
EC	electrochemical
EETs	epoxyeicosatrienoic acids
ERK	extracellular signal–regulated kinase
grad	gradient
H_2S	Hydrogen sulfide
$K_{Ca}3.1$, sK4, IK1	intermediate-conductance Ca^{2+}-activated K^+ channel
IP_3	inositol-1,4,5-trisphosphate
K_{IR}	inward-rectifier K^+
IP_3R	IP_3 receptors

E_K	K^+ equilibrium potential
$Ca_V1.2$	L-type voltage-gated Ca^{2+} channels
BK_{Ca}	large-conductance Ca^{2+}-activated K^+
LRRCs	leucine-rich-repeat-containing proteins
mTOR	mammalian target of rapamycin
MEK	mitogen-activated protein kinase kinase
MuRF1	muscle RING finger protein 1
NOX5	NADPH oxidase 5
SKA-31	Naphtho[1,2-d]thiazol-2-ylamine
NOR-1	neuron-derived orphan receptor-1
NO	Nitric oxide
NF	Nuclear Factor
NFATC3	nuclear factor of activated T-cells, cytoplasmic 3
PDGF	platelet-derived-growth-factor
PKA	protein kinase A
PKC	Protein kinase C
PKG	protein kinase G
ROC	receptor operated channels
RCK	regulator of K^+ conductance
REST	repressor element 1-silencing transcription factor
RyR	ryanodine receptors
SOC	store-operated channels
SAC	stretch-activated channels
SUR	sulphonylurea receptors
TRP	transient receptor potential
TM	transmembrane
VSM	vascular smooth muscle
VGCC	voltage-gated Ca^{2+} channels
K_V	voltage-gated K^+

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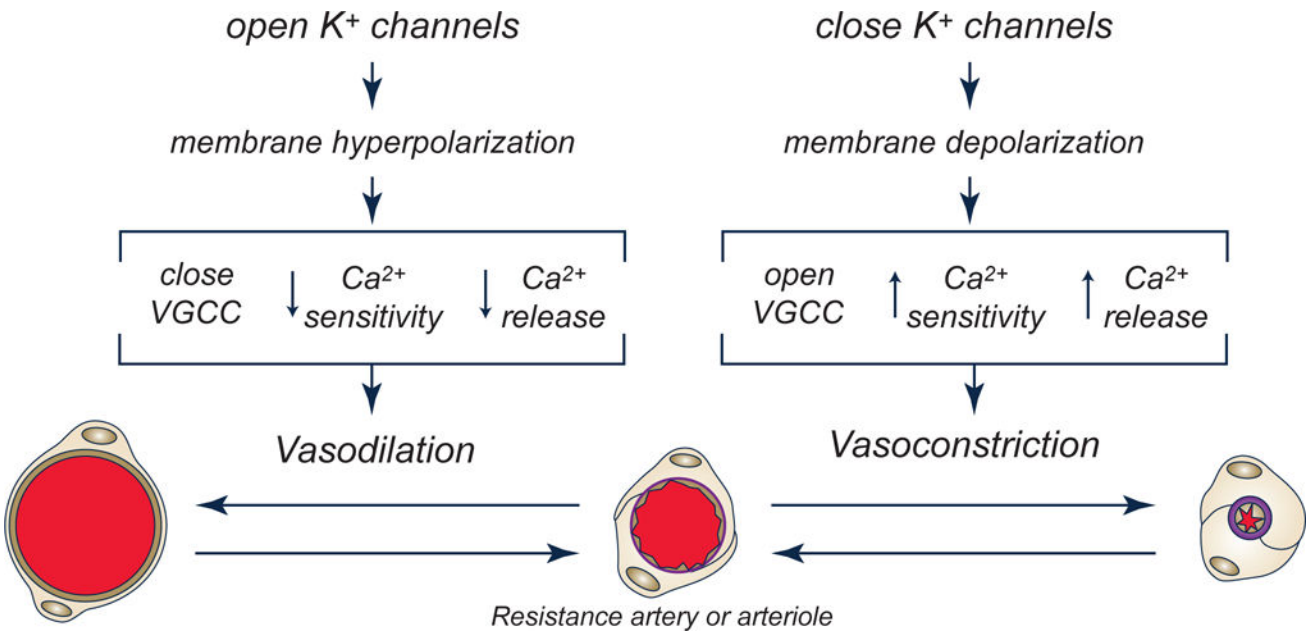

Figure 1.

Potassium channels regulate vascular smooth muscle contraction. Schematic diagram outlining the effects of K^+ channel opening and closing on the membrane potential of VSM cells, which, in turn, affects processes that lead to relaxation or contraction of VSM leading to vasodilation or vasoconstriction. Voltage-gated Ca^{2+} channels (VGCC). See text for more information. Modified from (Jackson, 2005).

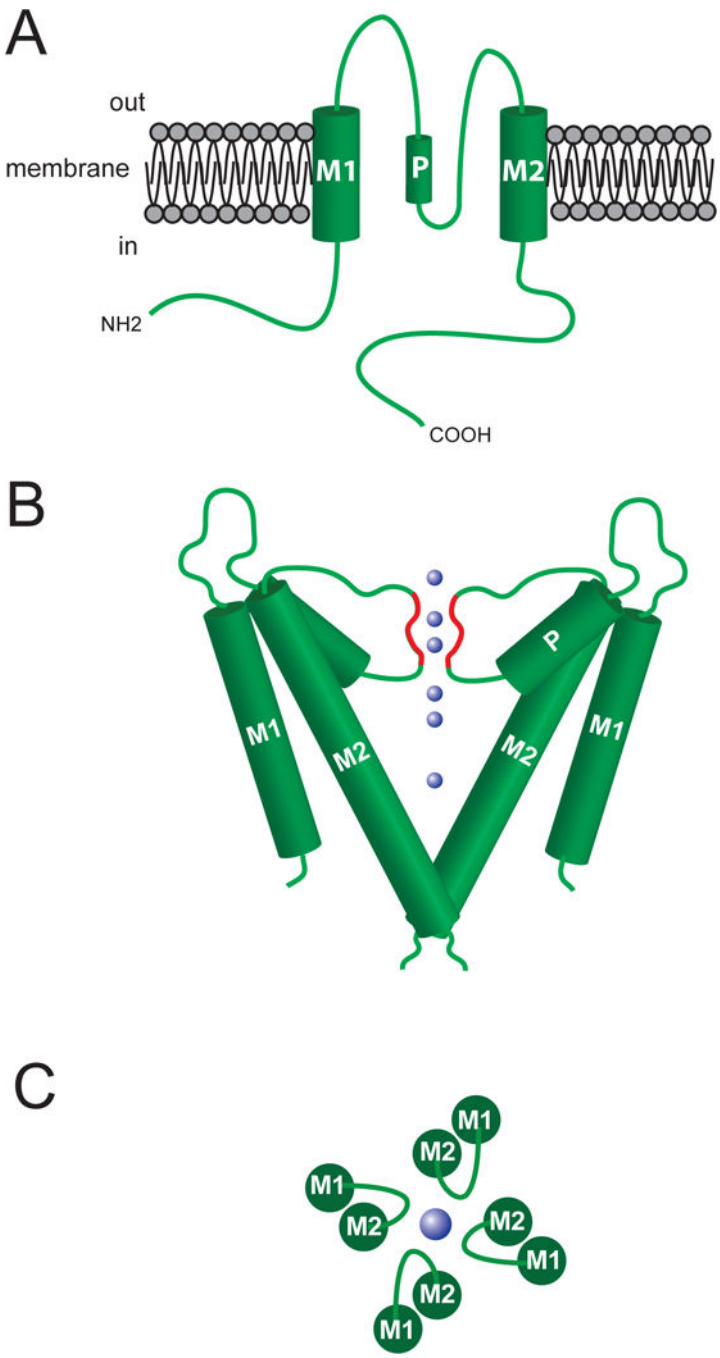

Figure 2.

Structure of the ion conducting pore of K^+ channels. Top panel (A) shows a schematic representation of a two membrane spanning domain (M1 and M2) K^+ channel. Functional channels are formed from a tetramer of these units, with the ion-conducting pore being formed by M2 and the P-loop domain that connects M1 and M2 (P in figure refers to the pore helical domain). Middle panel (B) shows approximate orientation of two sets of the M1, M2 and P-loops forming the channel. The blue spheres represent K^+ ions, and the red highlighted regions of the P-loops represent the selectivity filter of the channel's pore. The

bottom panel (C) shows a top view of the channel subunits and the P-loop forming the K^+ ion-conducting pore. See text for references.

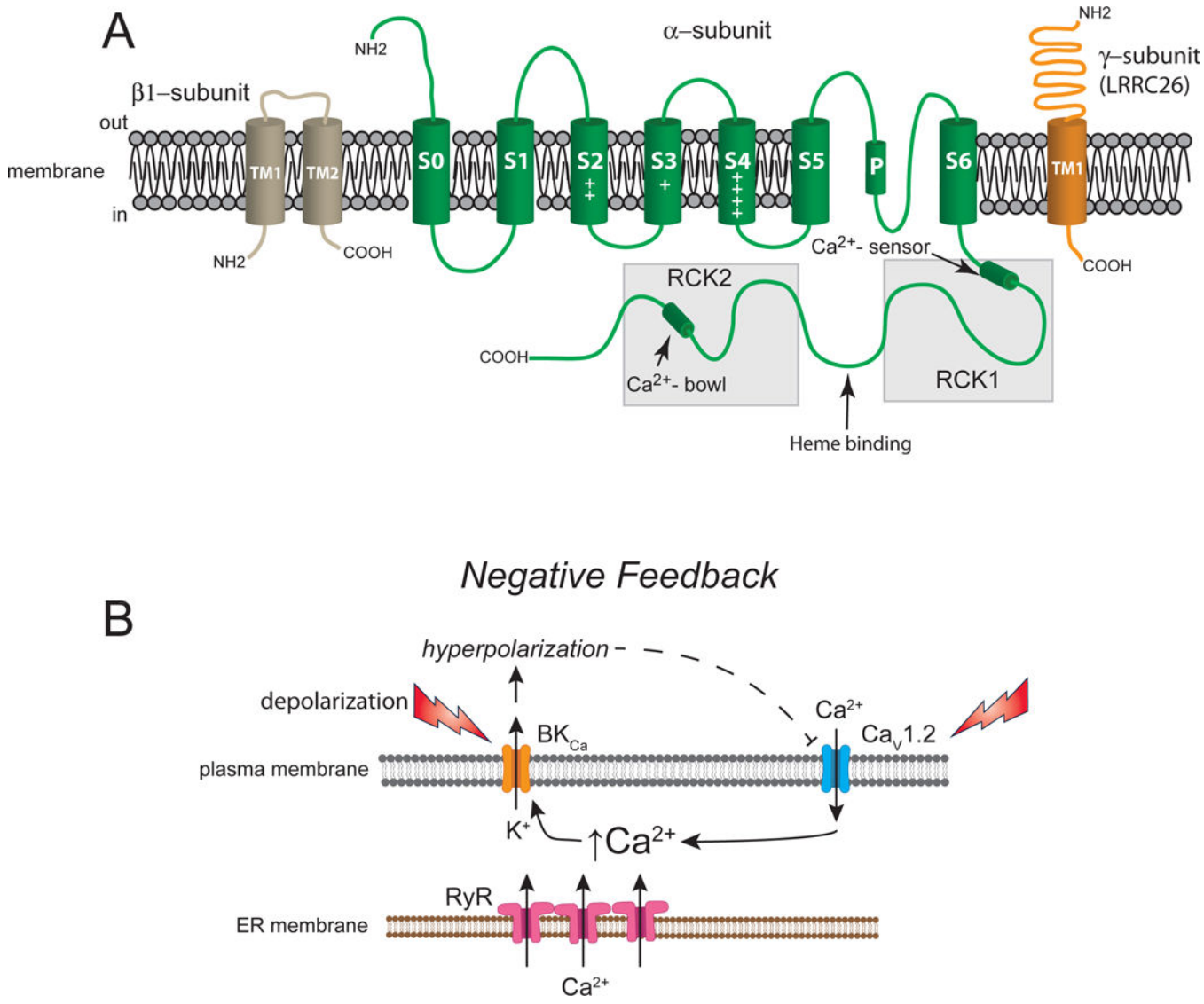

Figure 3.

Vascular BK_{Ca} channels. Panel A shows a β_1- subunit with two membrane-spanning domains, one pore-forming α-subunit with seven membrane-spanning domains and a γ-subunit (LRRC26, for example) with one membrane-spanning domain. Panel B shows a schematic of the primary negative feedback role for BK_{Ca} channels in contractile VSM. Membrane depolarization (due to activation of other membrane channels, not shown), or increases in intracellular Ca^{2+} in the vicinity of BK_{Ca} channels due to release of Ca^{2+} from ryanodine receptors (RyR, Ca^{2+} sparks), or influx of Ca^{2+} through L-type voltage gated Ca^{2+} channels ($Ca_V1.2$), results in activation and opening of BK_{Ca} channels. The efflux of K^+ through these channels leads to membrane hyperpolarization and closure of $Ca_V1.2$ channels, negative feedback regulation of VSM excitability.

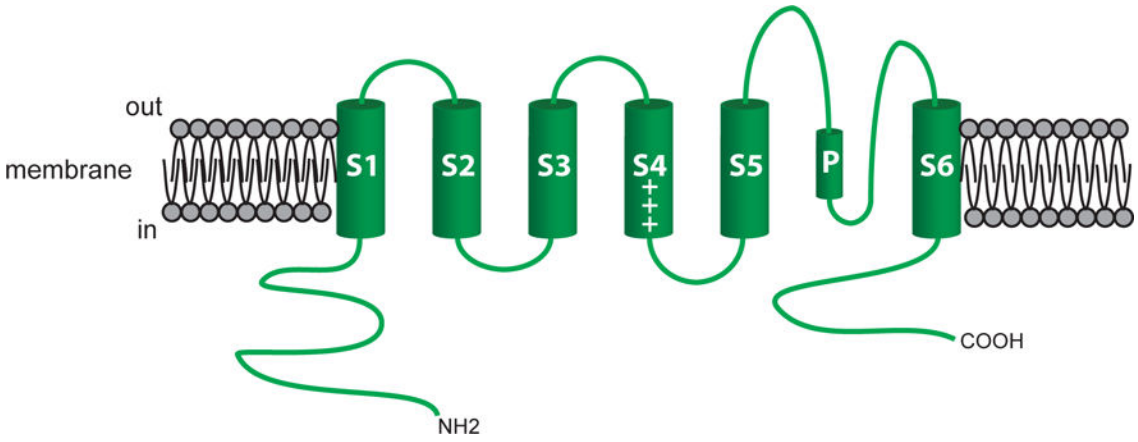

Figure 4.

The pore-forming α-subunit of K_V channels. Shown is a schematic of the 6 membrane spanning domains of a typical K_V channel. The length and composition of the carboxy (COOH) and amino (NH_2) varies among the large number of K_V channel isoforms expressed in VSM cells. See text for more information.

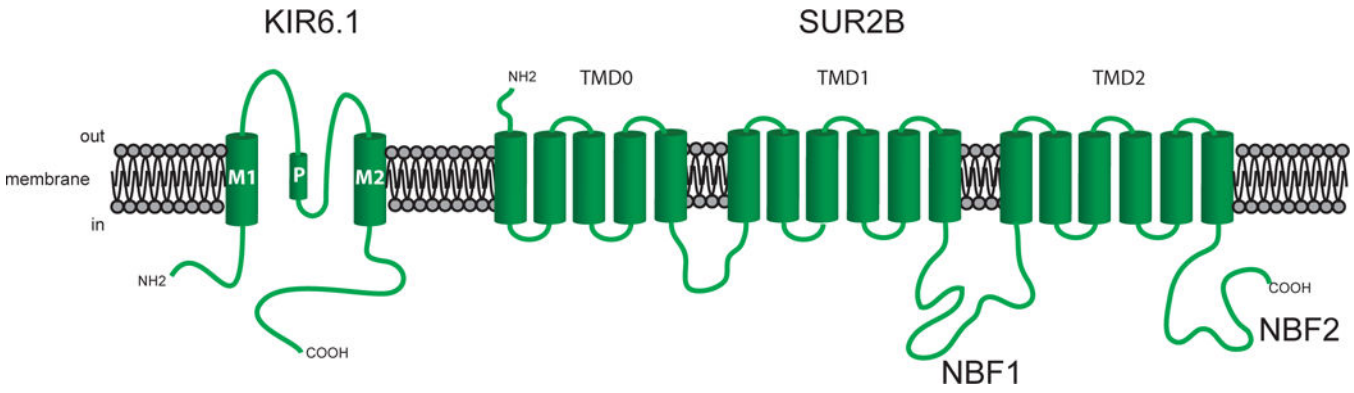

Figure 5.

Subunits of K_{ATP} channels. Shown are the $K_{IR}6.1$ and SUR2B subunits that are thought to comprise VSM K_{ATP} channels. The $K_{IR}6.1$ subunits have two membrane spanning domains, whereas the SUR2B subunits have seventeen membrane spanning domains clustered into three groups (TMD0, TMD1, TMD2), as shown. Functional channels are formed from a hetero-octamer of these two subunits. See text for more information and references.

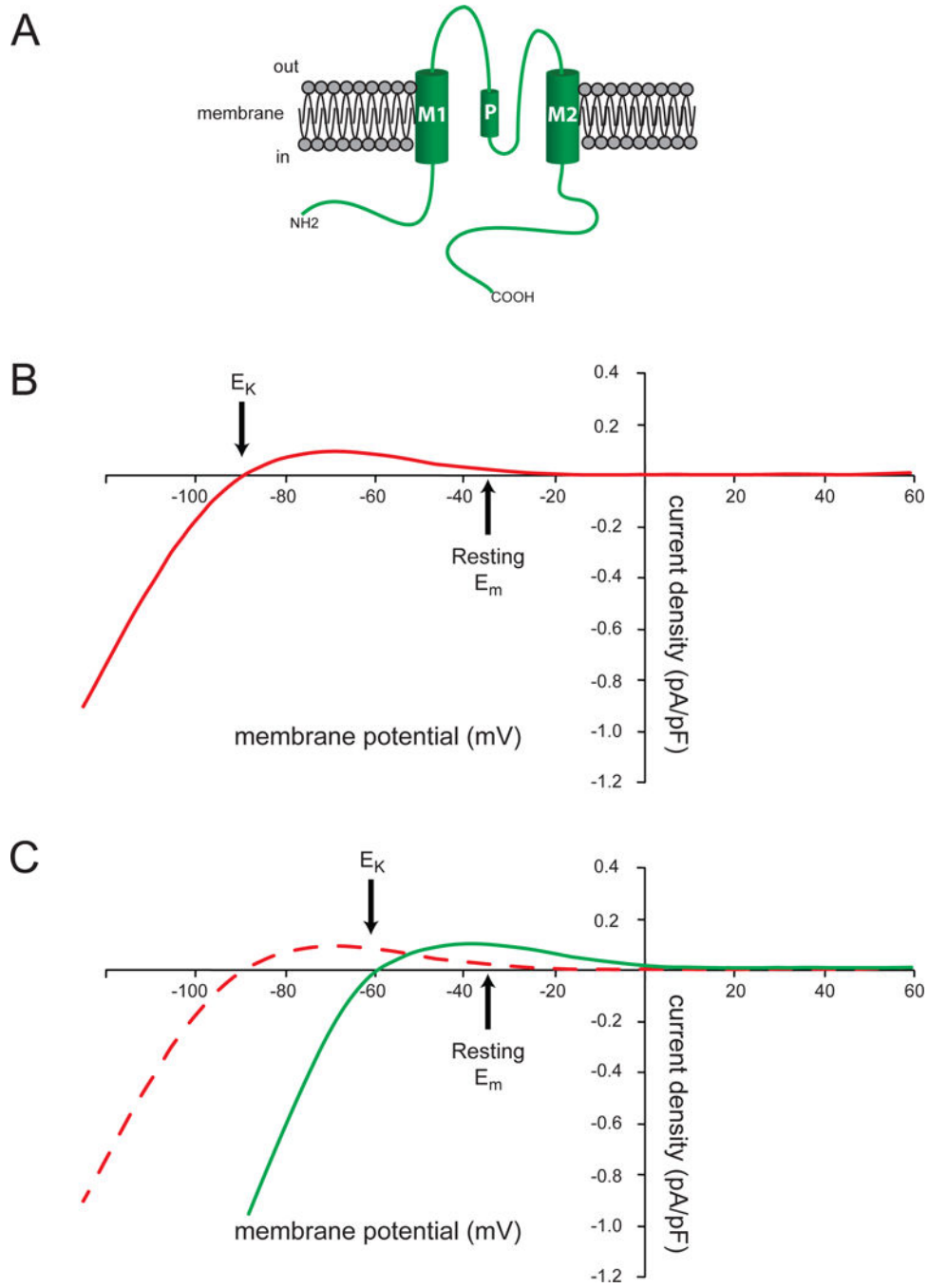

Figure 6.

Vascular K_{IR} channels and their currents. Panel A shows the topology of K_{IR} channels with two membrane spanning domains. Functional channels are composed of a tetramer these subunits (see Figure 2). Panel B shows a schematic of the current-voltage-relationship for VSM K_{IR} channels for a cell with 5 mM K^+ in the extracellular solution (140 mM K^+ intracellular) and is based on data from (Filosa et al., 2006). At membrane potentials more negative than the K^+ equilibrium potential (E_K, ~−90 mV in 5 mM K^+), the channel conducts K^+ into the cells, as shown by the negative current density values. At potentials

more positive than E_K up to ~−30 mV, K_{IR} channels conduct K^+ ions out of the cell, and contribute to the resting membrane potential as denoted by the small positive currents at the assumed resting membrane potential of −35 mV. Note that anything that hyperpolarizes the membrane will recruit outward, positive current through K_{IR} channels, effectively amplifying the initial hyperpolarization. Panel C demonstrates the effects of increasing extracellular K^+ from 5 mM (red dashed curve) to 15 mM K^+ (green solid curve): increased extracellular K^+ shifts the E_K from −90 mV to ~−60 mV. Note that there is now an elevated outward K^+ current at the original resting membrane potential. This enhanced outward K^+ current will hyperpolarize the VSM cell membrane from its resting value toward E_K, leading to vasodilation.

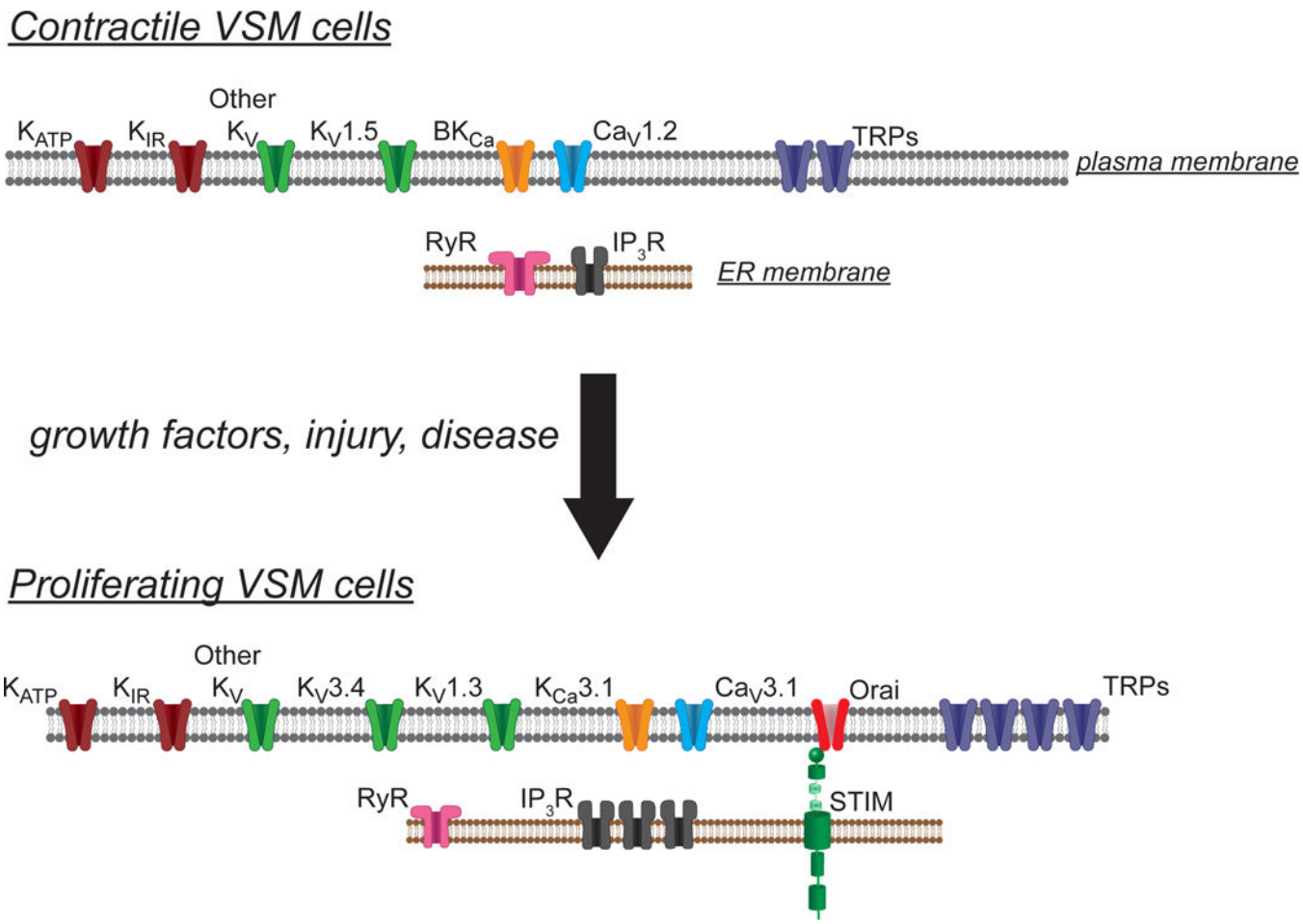

Figure 7.

Ion channel remodeling in proliferating VSM cells. Schematic summary of the ion channels expressed in contractile VSM cells and those expressed in proliferating VSM cells. Contractile VSM cells express predominantly L-type voltage-gated Ca^{2+} channels ($Ca_V1.2$), BK_{Ca} channels, and $K_V1.5$, in addition to K_{ATP}, K_{IR} and several additional types of K_V channels. A number of transient receptor potential channels (TRPs) also are expressed that contribute to store-operated, receptor operated and stretch-activated cation channels. Intracellular ryanodine receptors (RyR) and IP_3 receptors (IP_3R) also are expressed and functional in these cells. In response to growth factors, injury or disease, the pattern of expression of ion channels is remodeled. Proliferating VSM cells lose expression of $Ca_V1.2$, BK_{Ca} and $K_V1.5$ channels. In their place, T-type Ca^{2+} ($Ca_V3.1$), $K_{Ca}3.1$, $K_V1.3$ and $K_V3.4$ channels are expressed. Proliferating cells also upregulate expression and function of store-operated channels (Orai/STIM), TRP channels and IP_3R. See text for more information.

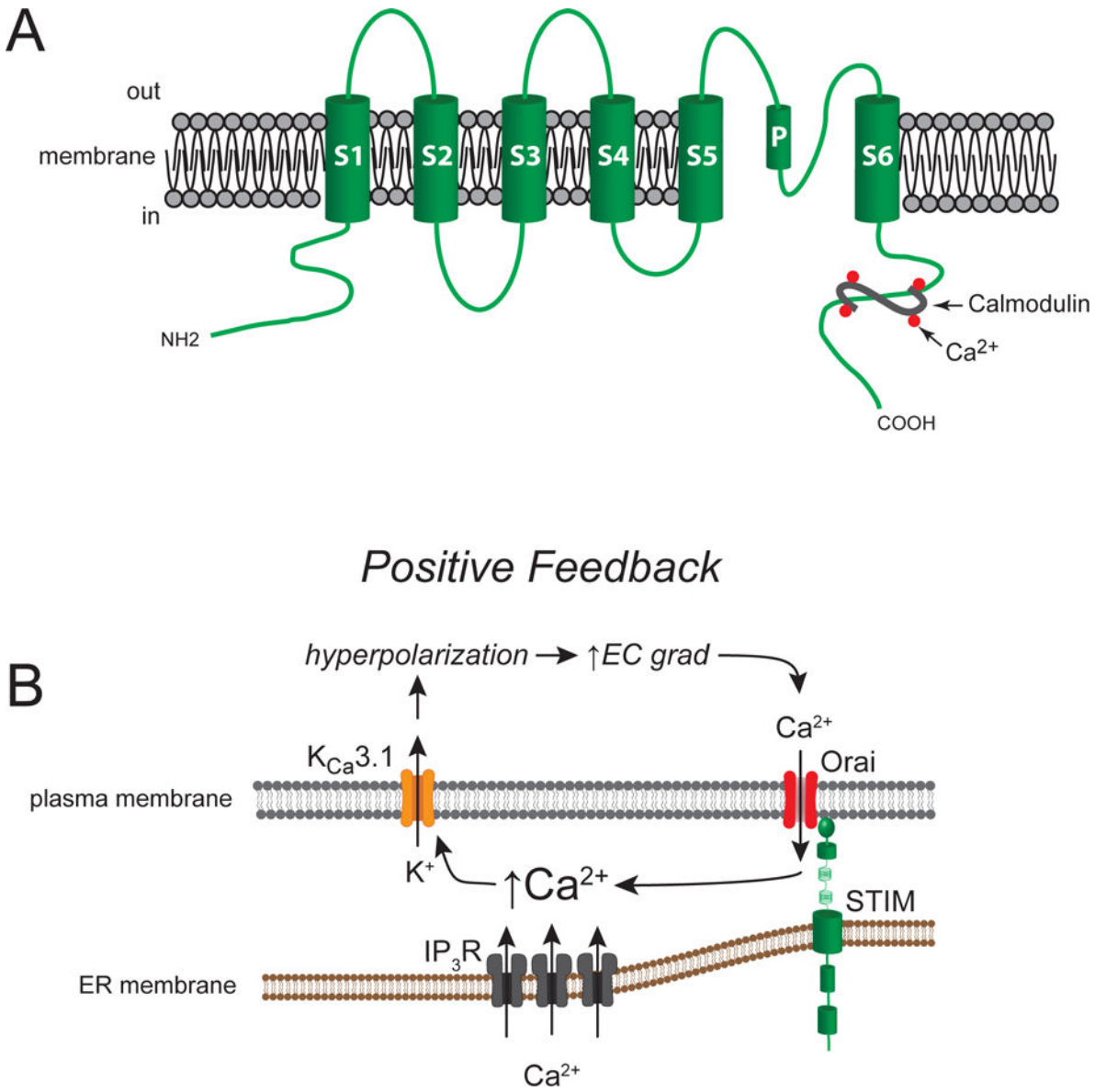

Figure 8.

Vascular $K_{Ca}3.1$ channels and their function in proliferating VSM cells. Panel A shows a schematic of an α-subunit demonstrating the typical six-membrane spanning domain structure of $K_{Ca}3.1$ channels. Calcium sensitivity is conferred by the Ca^{2+}-binding protein, calmodulin, that binds to the channel's C-terminus. Panel B shows a schematic of the role played by $K_{Ca}3.1$ channels in proliferating VSM cells. In proliferating cells, store-operated Ca^{2+} channels, composed of Orai proteins and the Ca^{2+} -sensing protein, STIM, are up-regulated, as are IP_3R receptors. Increases in intracellular Ca^{2+} produced by increased activity of Orai/STIM and IP_3R, activates $K_{Ca}3.1$ channels, leading membrane hyperpolarization. This hyperpolarization increases the electrochemical (EC) gradient (grad) for Ca^{2+} diffusion into the cells, augmenting Ca^{2+} influx through Orai/STIM and other non-voltage-gated Ca^{2+} channels in proliferating cells, leading to an increase in intracellular

Ca^{2+}. This is a positive-feedback system, in contrast to the negative-feedback system that is found in contractile VSM cells (see Figure 3B).