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Pathophysiology of voltage-gated K^+ channels in vascular smooth muscle cells: Modulation by protein kinases

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ABSTRACT

In this review, the pathological alteration and clinical relevance of voltage-gated K^+ (Kv) channels and their specific regulation by protein kinase-dependent signaling in vascular smooth muscle cells are described, particularly focusing on the pulmonary vasculature. The physiological relevance, channel characteristics, pharmacological modulation, and expression of Kv channels vary between different arterial beds and between subdivisions of arteries within those vascular beds. Although detailed signaling cascades regulating Kv channels are not clearly elucidated, it is known that the Kv channels in vascular smooth muscle cells can be tightly regulated by protein kinases C (PKC) and A (PKA). Alterations in Kv channel expression and function has been noted in pathological and pathophysiological conditions including hypertension (pulmonary and systemic), in diabetes and in individuals subjected to prolonged hypoxia (high altitude living). Vascular Kv channels are potential therapeutic targets in diseases such as pulmonary arterial hypertension and, therefore, it is important to understand the specific pharmacological modulation of Kv channel isoforms in different vascular beds.

Contents

1. Introduction

K^+ channels are important effector proteins that have multiple functions in vascular smooth muscle. K^+ channels are required for the maintenance of vascular tone; controlling membrane potential and intracellular Ca^{2+} signaling to regulate vasoconstriction (Nelson and Quayle, 1995; Yuan, 1995; Ko et al., 2008). Vascular smooth muscle cells (SMC) express five functionally distinct types of K^+ channels: Ca^{2+}-activated K^+ (BK_{Ca}), ATP-sensitive K^+ (K_{ATP}), inward rectifier K^+ (Kir), voltage-gate K^+ (Kv) and two pore domain K^+ (K_{2P}) channels. Among these, Kv channels are postulated to be a major determinant of vascular tone and resting membrane potential (Yuan, 1995; Ko et al., 2008). This review summarizes the physiological role of Kv channels expressed in vascular SMC

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focusing on protein kinase-dependent regulation of Kv channels, disease related pathologies and clinical implications.

2. Kv channels in the vasculature

Kv channels are highly expressed in most vascular SMC. Activated by membrane depolarization, they allow an efflux of K^+ which serves, in part, to repolarize the membrane to the resting membrane potential (Fig. 1). A small depolarization in vascular SMC activates L-type voltage-dependent Ca^{2+} channels causing Ca^{2+} influx and stimulation of contractile filaments; therefore, activity of Kv channels is important for regulating cell excitability and maintaining basal tone (Nelson and Quayle, 1995; Korovkina and England, 2002).

Kv currents recorded in vascular SMC can be divided into two major types based on differences in the voltage dependence of activation and inactivation, kinetics, and sensitivity to inhibitors (Nelson and Quayle, 1995; Iida et al., 2005); they include the delayed rectifier outward K^+ current (I_K) and the transient outward K^+ current (I_A). I_K is fast activating with slow inactivation, whereas I_A shows a faster activation and rapid inactivation kinetics; both currents are voltage dependent (Beech and Bolton, 1989; Halliday et al., 1995). In pulmonary arterial SMC, I_K is proposed to be predominant in controlling the resting membrane potential due to its activation threshold close to the resting membrane potential (~ -40 mV) (Fleischmann et al., 1993; Ishikawa et al., 1997; Yuan et al., 1998a). I_A constitutes a relatively small portion of the total outward Kv current and is largely inactivated at a resting membrane potential (Yuan et al., 1998a; Xu et al., 1999). I_K is present in most vascular SMC, whereas I_A is less frequently detected; for example, I_A coexists with I_K in vascular SMC isolated from the renal resistance arteries (Gordienko et al., 1994), portal veins (Beech and Bolton, 1989), and the pulmonary artery (Clapp and Gurney, 1991; Smirnov and Aaronson, 1995).

Structurally, the Kv channel is a heteromultimeric protein composed of four pore-forming α-subunits and cytosolic accessory β-subunits. The Kv channel α-subunits are six transmembrane spanning domains (S1–S6) with pores between S5 and S6, containing the S4 voltage-sensing transmembrane domain (Jiang et al., 2003). Previous studies have reported a differential expression of Kv channel genes at the mRNA and protein levels in the vascular system (Yuan et al., 1998a; Xu et al., 1999, 2000). Such differential expression of Kv channel genes contributes to their distinct electrophysiological and pharmacological properties in vascular SMC. Heterotetrameric and homotetrameric association of Kv channel genes contributes to a vast array of Kv current phenotypes. Par way of example, a channel comprising of two Kv2.1 and two Kv1.5 subunits may functionally differ from a tetramer consisting of three Kv2.1 subunits and one Kv1.5 subunit; consequentially the native Kv currents dramatically differ in terms of kinetics, amplitude and response to drugs. Furthermore, tissue and species specific Kv gene expression contributes to the current heterogeneity. Kv1.2, Kv1.3, Kv1.4, Kv1.5, Kv2.1, Kv2.2, Kv3.2, Kv3.3, Kv3.4, Kv4.1, Kv4.2, Kv4.3, Kvβ1, Kvβ2, and Kvβ3 channel genes are expressed in rat mesenteric artery SMC (Xu et al., 1999), but the Kv1.1, Kv1.6, and Kv3.1 transcripts are not. However, Kv1.1 and Kv1.6 are expressed in rat pulmonary arterial SMC alongside Kv1.2, Kv1.4, Kv1.5, Kv9.3, Kvβ1, Kvβ2, and Kvβ3 (Yuan et al., 1998a). The discrepancy between species and artery location produces different channel kinetics including; 1) the voltage dependence of channel activation and inactivation, 2) different single-channel conductance, and 3) different sensitivity to inhibitors.

One distinguishing feature of Kv channel subtypes is their sensitivity to pharmacological modulators. Pharmacological tools most frequently to inhibit Kv channels are 4-aminopyridine (4-AP) and tetraethylammonium (TEA). In general, vascular SMC from most arteries demonstrate a greater sensitivity of Kv currents (I_{Kv}) to 4-AP; some arteries, such as the aorta, are also very responsive to TEA (Table 1). In fact, electrophysiological recordings have revealed that channels encoded by Kv1.2 and Kv1.5 genes are relatively sensitive to 4-AP (Overturf et al., 1994), whereas Kv2 channels are inhibited more effectively by TEA (Immke et al., 1999). Kv1.2 (Grissmer et al., 1994), Kv1.3, and Kv1.6 (Garcia et al., 1994) channels are quite sensitive to charybdotoxin, commonly used to inhibit BK_{Ca} channels, on the other hand, Kv1.5 (Grissmer et al., 1994) and Kv2.1 (Garcia et al., 1994) channels are not. The sensitivity differences might be attributed to a differential expression of Kv channel subtypes, animal species, gender, cell isolation techniques, or recording conditions.

Differences in Kv channel kinetics, pharmacology and diversity are also evident during development. For example, the resting membrane potential in fetal sheep pulmonary arterial SMC is regulated by BK_{Ca} channels; charybdotoxin depolarizes the resting membrane potential (Reeve et al., 1998). However, in adults, the Kv current amplitude is predominant under resting conditions and the resting membrane potential is only depolarized by application of 4-AP, not TEA or charybdotoxin. Additionally, Belevych et al. (2002) suggested that Kv channels in neonatal rat aortic SMC are blocked by 4-AP, but are insensitive to a high concentration of TEA (10 mM), whereas, in adult cells the opposite holds true.

In addition to variation in the expression of Kv channels and channel isoforms between different vascular beds, differences are also observed among different arterial branches within a particular vascular bed. Expression differences are associated with a distinct Kv current phenotype diversity. In rat pulmonary arterial SMC, two populations of Kv channels are present in conduit arteries: 4-AP-

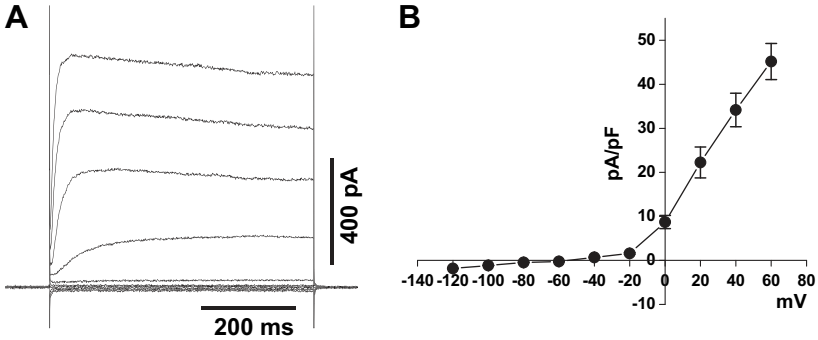

Fig. 1. Voltage-dependent K^+ (Kv) channels in rabbit coronary arterial SMC. (A) Superimposed current traces were elicited by depolarizing step pulses from −120 mV to +60 mV with a holding potential of −60 mV in steps of 20 mV for 600 ms. (B) Current–voltage (*I–V*) relationship of Kv channels. Reproduced with kind permission from Park et al. (2005a).

Table 1
Potency of Kv channel inhibitors 4-aminopyridine (4-AP) and tetraethylammonium (TEA) in a variety of vascular SMC.

	4-AP (IC_{50}) mM	TEA (IC_{50}) mM
Aorta	5.9 (Tammaro et al., 2004) 3.2 (Heaps et al., 2005)	3.1 (Tammaro et al., 2004)
Coronary	1.4 (Remillard and Leblanc, 1996) ~10 (Volk et al., 1991)	~10 (Ishikawa et al., 1993) ~10 (Volk et al., 1991) ~1 (Heaps et al., 2008)
Mesenteric	~1 (Smirnov and Aaronson, 1992) 5.1 (Xu et al., 1999: Lu et al., 2001)	9.9 (Xu et al., 1999; Lu et al., 2001)
Pulmonary	0.3 (Okabe et al., 1987) >10 (Ko et al., 2007)	>100 (Okabe et al., 1987) 1–5 (Ko et al., 2007)
Cerebral	~2 (Robertson and Nelson, 1994)	>10 (Robertson and Nelson, 1994)

sensitive (IC_{50}; 232 μM), which are almost insensitive to TEA, and TEA-sensitive (IC_{50}; 2.6 mM), which are relatively insensitive to 4-AP. The smaller diameter, resistance arteries uniformly have a third type of 4-AP-sensitive Kv channels (IC_{50}; 352 μM, Smirnov et al., 2002). Another study supported this hypothesis finding that the Kv current amplitude in resistance pulmonary arterial SMC is predominant and sensitive to 4-AP compared with conduit arteries (Archer et al., 1996, 2004).

3. Regulation of Kv channels by protein kinases

Although it is widely accepted that vasodilators such as bosentan, a competitive and non-selective endothelin receptor (ET_A and ET_B) inhibitor, and vasoconstrictors such as endothelin-1, arginine vasopressin and thromboxane exert their vasoactive influence, in part, by regulation of Kv channels, there are only a few studies which have investigated the mechanism involved. The diagram in Fig. 2 summarizes such studies. Most studies agree that vasoconstrictor-induced Kv channel inhibition is mediated by the activation of phospholipase C (PLC) and protein kinase C (PKC). Serotonin, for example, inhibits the Kv currents in pulmonary vascular SMC concomitant with membrane depolarization and mediated by the activation of PLC, PKC and tyrosine kinases; a study by Cogolludo et al. (2006) used U73122 and Gö6976 to inhibit PLC and classic diacylglycerol-sensitive PKCs and found that serotonin-induced Kv current inhibition was prevented (Cogolludo et al., 2006). The same group also showed that thromboxane A_2-induced inhibition of the Kv channels leads to membrane depolarization and, consequently, to pulmonary vasoconstriction via the activation of PKCζ. Tyrosine kinase and Rho kinase, however, were not involved in the thromboxane A_2 response. Angiotensin II and endothelin-1 inhibited Kv currents in mesenteric and pulmonary arterial SMC, respectively, and these inhibitory effects were completely dependent on the activation of Ca^{2+}-independent PKC subtypes (mainly the ε subtype) and somewhat dependent on the inhibition of protein kinase A (PKA) (Shimoda et al., 1998; Hayabuchi et al., 2001). On the other hand, β-adrenoceptor stimulation activates Kv currents by activating PKA in vascular SMC isolated from the rabbit portal vein (Aiello et al., 1995; Standen and Quayle, 1998). Furthermore, other known vasodilators, such as prostacyclin and adenosine, activate the Kv currents in rabbit cerebral and coronary arterioles, respectively (Dong et al., 1998; Heaps et al., 2008). To date, few studies have investigated the modulation of Kv channels by protein kinase G (PKG).

Specific inhibitors/agonists for protein kinases are indispensible tools for studying the modulation of Kv channel by various protein kinases. There is significant variability in the actions of protein kinase modulators between different vascular beds (Table 2). The most widely used PKC inhibitor, bisindolylmaleimide (I) (BIM) has been reported to directly inhibit the Kv channels in coronary and mesenteric arterial SMC in a phosphorylation-independent, and voltage-, time-, and use-

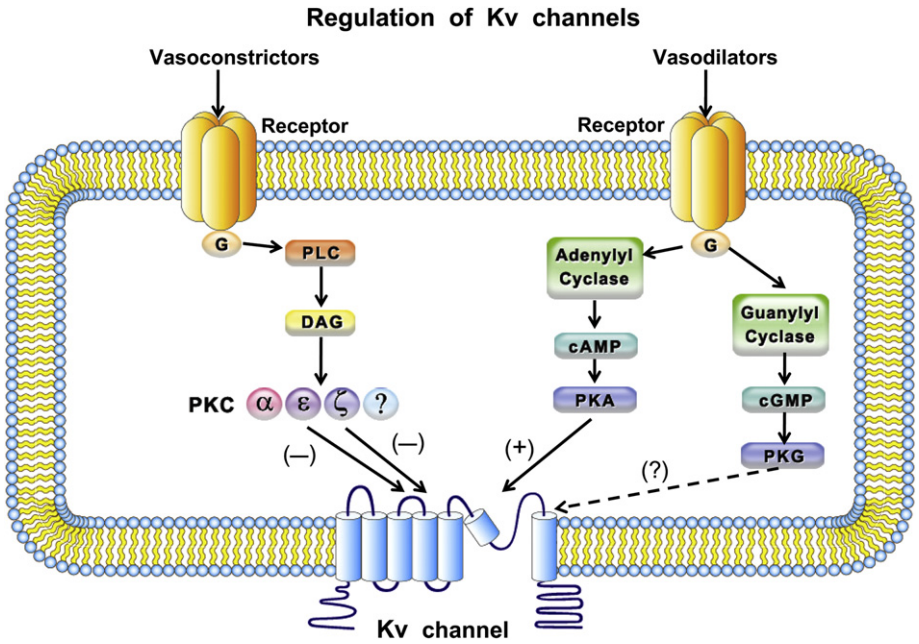

Fig. 2. Schematic of the proposed Kv channel modulation mechanisms by vasoconstrictors or vasodilators in vascular SMC. Vasoconstrictors stimulate the G-protein coupled receptors, which cause PLC-DAG activation and, consequently, activate various PKC isoforms (α, ε, ζ) that induce Kv channel inhibition. Vasodilators also stimulate G-protein coupled receptors and inducing the activation of either adenylyl cyclase or guanylyl cyclase. The activation of adenylyl cyclase causes cAMP production, which activates PKA, resulting in an increase in Kv channel activity. Activation of guanylyl cyclase, which leads to an increase in cGMP production and PKG activity, has also been shown to increase Kv channel activity. PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C; PKA, protein kinase A; PKG, protein kinase G.

Table 2
Effect of protein kinase inhibitors on Kv channels in the vasculature.

	Tissue	IC_{50} (μM)	Block pattern	References
Bisindolylmaleimide (I)	Mesenteric	0.23	Open-, voltage-, time-, use-dependent block	Kim et al., 2004
	Coronary	0.27		Park et al., 2005b
	CHO (Kv1.5)	0.38		Choi et al., 2000
Staurosporine	Coronary	1.35	Open-, voltage-, time-, use-dependent block	Park et al., 2005a
	CHO (Kv1.3)	1.20		Choi et al., 1999
H-89	Coronary	1.02	Blocking the pore cavity directly (Coronary) or open block (Kv1.3)	Son et al., 2006
	CHO (Kv1.3)	1.70		Choi et al., 2001
Genistein	Coronary	7.51	Use-dependent and direct block	Ko et al., 2009
	CHO (Kv3.1)	15.71		Choi et al., 2006
	Ventricle	~30		Washizuka et al., 1998

dependent fashion (Kim et al., 2004; Park et al., 2005a; Fig. 3). Another non-specific PKC inhibitor, staurosporine also inhibits the Kv channel in coronary arterial SMC by a similar mechanism to BIM (Park et al., 2005b). BIM and staurosporine respectively inhibit Kv1.5 and Kv1.3 channels stably expressed in Chinese hamster ovary (CHO) cells (Choi et al., 1999, 2000). H-89 (*N*-[2-(*p*-bromocinnamylamino)ethyl]-5-isoquinolinesulfonamide, a known PKA inhibitor), has direct effects on the Kv channel from coronary arterial SMC and the Kv1.3 channel expressed in CHO cells (Choi et al., 2001; Son et al., 2006). Although the inhibition by H-89 on Kv1.3 expressed cells is due to an open-channel block, the inhibitory mechanism on coronary arterial SMC has been suggested to be the result of a direct block of the pore cavity. The different inhibitory mechanisms on Kv channels by H-89 between native vascular SMC (blocking pore) and Kv1.3 expressed cells (open-channel block) may be due to the recording of Kv channels formed from a variety of α-subunits. Another protein kinase inhibitor, genistein, inhibits the Kv channel in a use-dependent and direct block manner in coronary arterial SMC (Ko et al., 2009). In non-vascular cells, including ventricular myocytes and Kv3.1 expressing CHO cells, genistein inhibits Kv channels independent of tyrosine kinase activity with a much higher IC_{50} of 30 μM and 15.7 μM, respectively (Washizuka et al., 1998; Choi et al., 2006).

4. Alteration of the Kv channel expression and function in pathological conditions

Because Kv channels regulate vascular tone, altered Kv channel expression and function is related to pathophysiological conditions such as systemic arterial hypertension (Martens and Gelband, 1996; Cox et al., 2001), hypoxic pulmonary vasoconstriction (Smirnov et al., 1994; Wang et al., 1997; Archer et al., 2001; Platoshyn et al., 2001), pulmonary arterial hypertension (Yuan et al., 1998b; Remillard et al., 2007), and diabetes (Liu et al., 2001; Li et al., 2004; Bubolz et al., 2005). Roles for K^+ channels in both systemic and pulmonary hypertension are now evident. Studies, in general, agree that pulmonary arterial hypertension is associated with decreased I_{Kv}; however, K^+ channel expression and function are less definitive in the systemic vasculature during hypertension.

4.1. Systemic hypertension

Utilizing animal models of hypertension, such as the spontaneously hypertensive rat and deoxycorticosterone acetate (DOCA) salt-induced hypertension models, both increased and decreased Kv and BK_{Ca} channel expression and function have been observed (Martens and Gelband, 1996; Bratz et al., 2005; Zhang et al., 2005;

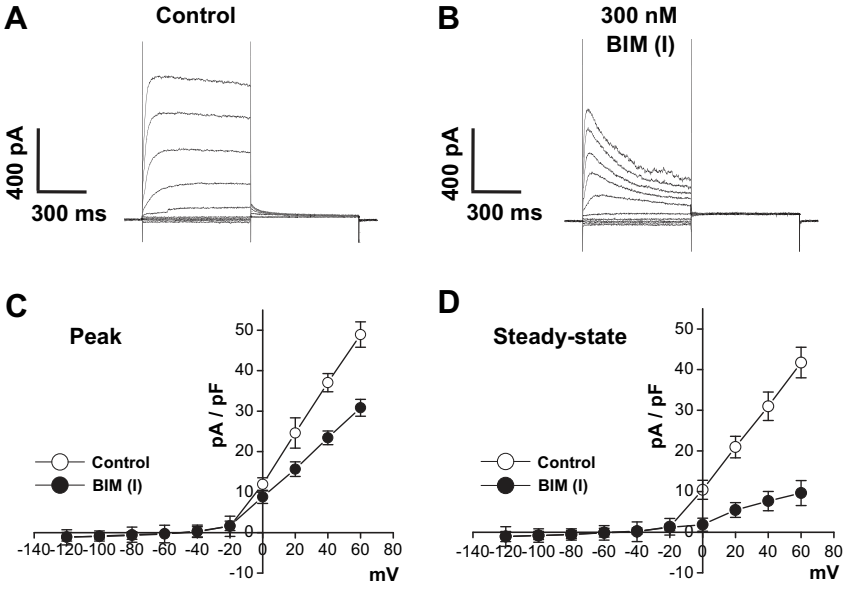

Fig. 3. Inhibitory effect of bisindolylmaleimide (I) on Kv currents from rabbit coronary arterial SMC. Superimposed currents were elicited by the same protocol as shown in Fig. 1 in the control condition (A) and in the presence of bisindolylmaleimide (I) (B). *I–V* relationship of the peak (C) and steady-state (D) Kv currents in the absence (○) and presence of bisindolylmaleimide (I) (●). Reproduced with kind permission from Park et al. (2005b).

Cox et al., 2001, 2008). In the renal vasculature, SMC exhibited a significantly depolarized membrane potential, increased angiotensin II-stimulated Ca^{2+} release and diminished Kv currents; a concomitant increase in BK_{Ca} currents was observed in the same cells (Martens and Gelband, 1996). Similar changes were observed in the mesenteric artery; decreased expression and function of Kv1.2 and Kv1.5 in conjunction with membrane depolarization were noted in Nώ-nitro-L-arginine induced hypertensive rats (Bratz et al., 2005). Furthermore, a decreased Kv current density with a predominant Ca^{2+} sensitive BK_{Ca} current accounting for the remaining outward K^+ currents was noted in SHR (Zhang et al., 2005). Unlike the renal vasculature and in the SHR model, BK_{Ca} channel expression and function in the mesenteric artery was decreased in the Nώ-nitro-L-arginine hypertension model. In complete contrast, Cox et al. (2001) reported that the mRNA level of Kv1.2, Kv1.3, and Kvβ1.1 was greater in thoracic aorta, tail and mesenteric artery SMC of SHR compared with the Wistar–Kyoto (WKY) control group. In addition, they found increases of Kv current density and a negative shift in the voltage dependence of activation in SHR. Because Kv channels play a major role in the regulation of the membrane potential, Cox et al. (2001) suggested that this increased Kv gene expression in SHR may be a compensatory response to normalize membrane potential and Ca^{2+} influx. Furthermore, in a subsequent study, they suggested that this altered gene expression during hypertension was not necessarily correlated with protein expression (Cox et al., 2008), and that differential expression of Kv subunits between SHR and WKY was tissue specific. For example, in both mesenteric and tail arteries, Kv1.2 and Kv1.5 expression is higher in SHR than in WKY. However, in the case of Kv2.1, the protein expression is higher in mesenteric, but lower in tail arteries of SHR. The protein expression of these channels in the thoracic aorta SMC remained unchanged in SHR (Cox et al., 2001, 2008).

4.2. Pulmonary arterial hypertension

In the pulmonary vasculature, dysfunction of Kv channels, in particular the expression and function of the Kv1.5 channel, is an underlying feature of pulmonary hypertension (Yuan et al., 1998c; Pozeg et al., 2003; Remillard et al., 2007). In pulmonary arterial SMC, the resting membrane potential is significantly depolarized, Kv current density is reduced and less sensitive to Kv channel blocker 4-AP. Such an impairment of Kv channel function results in an increase in pulmonary vasoconstriction and pulmonary vascular remodeling due to the increased net cytoplasmic Ca^{2+} concentration. Pulmonary arterial hypertension develops as a consequence of sustained vasoconstriction and vascular remodeling.

The inhibited function and expression of Kv channels in pulmonary artery SMC also impacts the balance between cell survival and death. The processes of cell proliferation and apoptosis and tightly regulated to ensure the number of cells remains constant throughout life. Apoptosis is highly regulated cell death with two recognizable phases; cell shrinkage with apoptotic volume decrease (AVD) which precedes DNA fragmentation, caspase activation and mitochondrial membrane depolarization. Several studies have highlighted a central role for K^+ channels in both stages. Apoptosis is enhances and caspase activity increased when the Kv1.5 channel encoding gene, *KCNA5*, is over expressed in pulmonary artery SMC. Similarly, if 4-AP is used to inhibit Kv channels prior to induction of apoptosis by staurosporine treatment (staurosporine is a potent apoptosis inducer), AVD is substantially decreases and apoptosis reduced by 46% (Brevnova et al., 2004). Furthermore, overexpression of anti-apoptotic oncogene Bcl-2 causes a concomitant downregulation of Kv α-subunit mRNA expression and decreases K^+ efflux from the cell (Ekhterae et al., 2001).

In individuals exposed to chronic hypoxia, for example those living at high altitudes, altered Kv channel expression and function have also been observed. Exposure to chronic hypoxia decreases Kv channel gene transcription and expression, especially the Kv1.2, Kv1.5 and Kv2.1, which reduces Kv current amplitude in pulmonary arterial SMC (Wang et al., 1997; Archer et al., 1998, 2001). This causes the development of hypoxic pulmonary vasoconstriction and, consequently induces the pulmonary hypertension during chronic hypoxia.

4.3. Diabetes

Hyperglycemia underlies many of the vascular complications and abnormalities in diabetes (Way et al., 2001; Creager et al., 2003). Changes in Kv channel function in arteries exhibiting diabetic vascular dysfunction have been investigated (Liu et al., 2001; Li et al., 2004 Bubolz et al., 2005). In coronary arteries subjected to high (23 mM) glucose, the 4-AP sensitive currents and 4-AP-mediated contractile responses were significantly impaired (Liu et al., 2001). This particular study addressed the superoxide generated by high glucose and additionally showed that the Kv current density was partially restored by antioxidant treatment. Furthermore, it has been shown that Kv channel function is reduced in coronary arteries in a streptozotocin treated rat model of diabetes (Bubolz et al., 2005). Impaired Kv channel activity during high glucose leads to an attenuated Kv current response to vasoconstrictors or vasodilators. Rainbow et al. (2006), for example, showed that increasing the glucose concentration within the physiological range reversibly decreased Kv currents and prevented the ET-1 induced inhibition of Kv currents in mesenteric arterial SMC. Also, another report demonstrated that the ability of isoproterenol to increase Kv currents was abolished under high glucose in the coronary artery (Li et al., 2003). Isoproterenol activated adenylyl cyclase and increased production of cAMP, result in phosphorylation and the opening of Kv channels (Aiello et al., 1995). The 4-AP sensitive current density, however, was reduced without a change in cAMP level under the high glucose conditions.

5. Therapeutic approaches targeting the Kv channel

The altered expression and function of Kv channels associated with the vascular dysfunction that accompanies hypertension, exposure to prolonged periods of hypoxia, and diabetes makes them an attractive therapeutic target (Wang et al., 1997; Archer et al., 1998, 2001; Yuan et al., 1998b; Liu et al., 2001; Li et al., 2004; Bratz et al., 2005; Cox et al., 2008). In particular, the Kv1.5 or Kv2.1 channels are downregulated in the pulmonary artery SMC in humans with pulmonary arterial hypertension (Yuan et al., 1998c; Remillard et al., 2007) as well as in rats with chronic hypoxia-induced pulmonary hypertension (Platoshyn et al., 2001; Pozeg et al., 2003). Thus, the Kv channel has been considered as a potential target to reverse or regress pulmonary artery remodeling. Michelakis et al. (2001, 2002, 2003) have intensively studied a way to increase Kv channel expression accompanying pulmonary hypertension. They used two strategies to increases Kv channel expression in pulmonary arterial SMC; oral administration of the metabolic modulator dichloroacetate restored Kv2.1 expression, and adenoviral gene transfer increased expression of Kv2.1 channels in pulmonary hypertensive animals. Furthermore, a Kv1.5 gene transfer was effective for reducing pulmonary hypertension (Pozeg et al., 2003). Besides impaired vascular function, it has been suggested that specific subtypes of Kv inhibition are therapeutic targets for pathological diseases, such as problems with cardiac

repolarization and insulin release. Reduced K^+ current density and expression of Kv1.5 were observed in patients with chronic atrial fibrillation (Van Wagoner et al., 1997), and reduced K^+ current density and Kv4.3 mRNA in human with heart failure (Kääb et al., 1998). Also, Kv2.1 has been suggested as a candidate ion channel target in the treatment of pancreatic beta cell insulin secretion; disruption of the Kv2.1 gene is associated with impaired insulin secretion (Herrington et al., 2006; Zhuang et al., 2009). Guangxitoxin, which is a peptide inhibitor of Kv2.1/Kv2.2 channels (Herrington et al., 2006) and synaptosomal protein of 25 kD, 206 amino acids (SNAP-25) both modulate Kv2.1 channel gating properties (Zhuang et al., 2009). It may be that reducing the function of a specific K^+ channel subunit could be an efficient way to develop a new drug, depending on the specific disease. However, a large number of K^+ channels have similar properties; thus, there is a limit to the use of specific inhibitors to target a specific type of Kv channel for a vascular disease. Currently, Kv channel blockers are non-specific, affecting multiple Kv channel subtypes. The Kv channel inhibitor, 4-AP effectively blocks most Kv subtypes, whereas correolide blocks Kv1.3 homotetramers, in addition to tetramers assembled from each of the classical Kv1-family members (Kv1.1–1.6) (Felix et al., 1999). To overcome this limitation, a specific antibody was developed to dissect gene subtypes from whole currents. Using this technique, several studies have evaluated distinct Kv channel subtypes from native whole cell Kv currents (Lu et al., 2002). However, to date, trials for clinical therapy including gene transfer and antibody targeting on Kv channel subtypes have problems with safety, tissue-specificity, and Kv subtype-selectivity that remain to be elucidated.

6. Conclusion

The role of Kv channels invascular SMC has attracted researchers due to the discovery of K^+ channel dysfunction in a variety of vascular diseases. Given the vast array of homo and hetero multimeric Kv channels present in the vasculature, it is difficult to study any channel in isolation, all currently available channel modulators are relatively non-selective. The development of more selective pharmacological tools to activate and inhibit vascular K^+ channels would significantly enhance our understanding of their role both at rest and during disease. More precise targeting of specific Kv channel subtypes may open new doors for the treatment of vascular disease with associated Kv channelopathy.

Acknowledgments

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