

Hiroshi Kuriyama Award 2007 Memorial Review**Physiological roles of K⁺ channels in vascular smooth muscle cells**

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Abstract

In this review, we present the basic properties, physiological functions, regulation, and pathological alterations of four major classes of K⁺ channels that have been detected in vascular smooth muscle cells. Voltage-dependent K⁺ (K_v) channels open upon depolarization of the plasma membrane in vascular smooth muscle cells. The subsequent efflux of K⁺ through the channels induces repolarization to the resting membrane potential. Changes in the intracellular Ca²⁺ concentration and membrane depolarization stimulate large-conductance Ca²⁺-activated K⁺ (BK_{Ca}) channels, which are thought to play an important role in maintaining the membrane potential. ATP-sensitive K⁺ (K_{ATP}) channels underscore the functional bond between cellular metabolism and membrane excitability. The blockade of K_{ATP} channel function results in vasoconstriction and depolarization in various types of vascular smooth muscle. Inward rectifier K⁺ (Kir) channels, which are expressed in smooth muscle of the small-diameter arteries, contribute to the resting membrane potential and basal tone. Kir channel activation has been shown to raise the extracellular K⁺ concentration to 10–15 mM, resulting in vasodilation. Each of K⁺ channels listed above is responsive to a number of vasoconstrictors and vasodilators, which act through protein kinase C (PKC) and protein kinase A (PKA), respectively. Impaired K_v, K_{ATP}, and Kir channel functions has been linked to a number of pathological conditions, which may lead to vasoconstriction.

Key words: K⁺ channels, vascular smooth muscle, protein kinase C, protein kinase A, protein kinase G

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Introduction

K⁺ channels contribute to the regulation of the membrane potential in electrically excitable cells, including those found in smooth muscle. Membrane hyperpolarization due to an efflux of K⁺ results from the opening of K⁺ channels in vascular smooth muscle. This effect is followed by the closure of voltage-dependent Ca²⁺ channels, leading to a reduction in Ca²⁺ entry, and vasodilation (Nelson and Quayle, 1995). In contrast, inhibition of K⁺ channels function leads to membrane depolarization and vasoconstriction. To date, four distinct types of K⁺ channel have been identified in vascular smooth muscle: voltage-dependent K⁺ (Kv) channels, Ca²⁺-activated K⁺ (BK_{Ca}) channels, ATP-sensitive K⁺ (K_{ATP}) channels, and inward rectifier K⁺ (Kir) channels (Nelson and Quayle, 1995; Standen and Quayle, 1998). The fundamental properties of these channels, as well as their responses to various stimuli including vasoconstrictors and vasodilators, and their associated signal pathways have been described in several reports.

In this review, we present a comprehensive summary of the current state of knowledge concerning each of the four major types of K⁺ channel in the vasculature.

Basic properties of K⁺ channels

Voltage-dependent K⁺ channels (Kv channels)

Broad voltage-dependent K⁺ (Kv) channels expression has been detected in vascular smooth muscle cells (e.g., Beech and Bolton, 1989a; Cox and Petrou, 1999). Kv channels open to allow an efflux of K⁺ in response to depolarization of the membrane potential (Fig. 1A), resulting in repolarization and a return to the resting membrane potential. Small-scale depolarization in vascular smooth muscle cells leads to an influx of Ca²⁺ through L-type Ca²⁺ channels and activation of the contractile machinery. Taken together, this indicates that Kv channels function to limit membrane depolarization and maintain resting vascular tone (Nelson and Quayle, 1995; Sobey, 2001; Korovkina and England, 2002).

The Kv channel inactivation results from sustained depolarization. Compared to the process of activation, Kv channel inactivation is relatively slow and involves an initial peak in the Kv current due to voltage-dependent activation followed by a drop in the current due to voltage-dependent inactivation (Nelson and Quayle, 1995). Steady-state Kv channel activation can be described using the Boltzmann equation: $y = 1 / \{1 + \exp(-(V - V_{1/2}) / k)\}$, where k is the slope factor, V is the test potential, and $V_{1/2}$ is the voltage require for half-maximal conductance (Park *et al.*, 2005a, 2005b). Using this equation, Kv channels in arterial smooth muscle cells have been shown to have k -values between 9 and 11 and to display half-maximal activation at voltages between -6 to -15 mV (Volk *et al.*, 1991; Robertson and Nelson, 1994; Nelson and Quayle, 1995; Park *et al.*, 2005a, 2005b). Similarly, Kv channel inactivation can be described using another Boltzmann equation: $y = 1 / \{1 + \exp((V - V_{1/2}) / \kappa)\}$ where V is the preconditioning potential, $V_{1/2}$ is the half-inactivation potential, and κ is the slope value (Park *et al.*, 2005a, 2005b). Based on these definitions, k -values between 5 and 11 and half-maximal inactivation values between -25 to -45 mV have been recorded for Kv channels (Volk *et al.*, 1991; Robertson and Nelson, 1994; Nelson and Quayle, 1995; Park *et al.*, 2005a, 2005b).

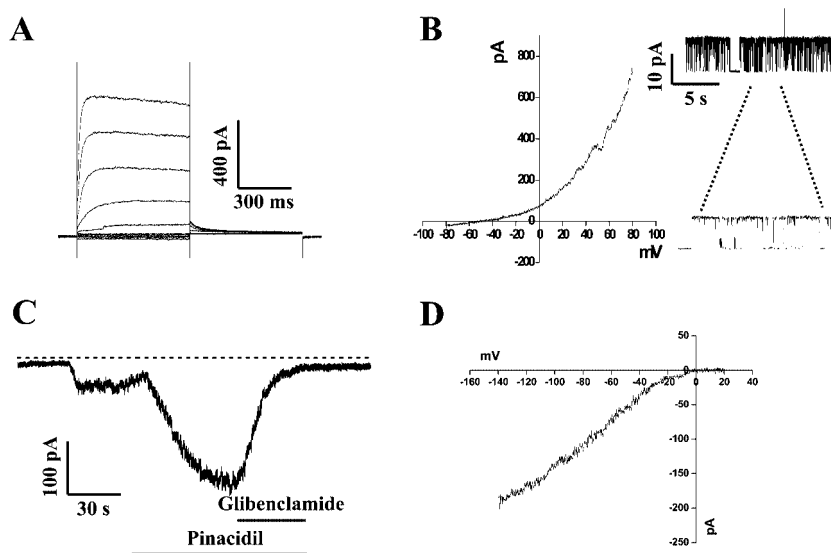


Fig. 1. K⁺ channels in coronary arterial smooth muscle cells. (A) Voltage-dependent K⁺ (K_v) currents in rabbit coronary arterial smooth muscle cell. Superimposed current traces are shown for 600-ms depolarizing pulses from -80 mV to voltages between -120 mV and +60 mV in steps of 20 mV. Data from Park *et al.* (2005b). (B) Ca²⁺-activated K⁺ (BK_{Ca}) channels in rabbit coronary arterial smooth muscle cells. The traces of the whole-cell currents and single-channel currents are shown in *left* and *right* panel, respectively. Data from Park *et al.* (2007a). (C) ATP-sensitive K⁺ (K_{ATP}) channels in rabbit coronary arterial smooth muscle cells. Recording of whole-cell current from a cell that was held at -60 mV, showing pinacidil activation of glibenclamide-sensitive K⁺ currents. Data from Park *et al.*, (2005d). (D) Inward rectifier K⁺ (Kir) channels in rabbit small-diameter coronary arterial smooth muscle cells. Current-voltage relationships of 50 μM Ba²⁺-sensitive currents in symmetrical K⁺ (140 mM). Data from Park *et al.* (2005e).

Divergent results have been obtained concerning the single-channel conductance of the K_v channels in vascular smooth muscle cells. For example, single-channel conductances of 5 and 8 pS were recorded in rabbit portal vein using physiological concentration of K⁺ (i.e., between 4 and 6 mM) (Beech and Bolton, 1989b), whereas a conductance of 6.5 pS was obtained using pig portal vein (Karle *et al.*, 1998). Moreover, conductances of 4.4, 7.3, and 5.5 pS have been reported for rabbit cerebral, coronary, and basilar arteries, respectively (Volk and Shibata, 1993; Robertson and Nelson, 1994; Nelson and Quayle, 2005). Contradicting these reports, larger slope conductance in rabbit coronary artery was found to be 70 pS at 140 mM [K⁺]_o, while that in canine renal artery was 57 pS at 5.4 mM [K⁺]_o (Gelband and Hume, 1992; Ishikawa *et al.*, 1993; Nelson and Quayle, 1995).

The various constituents of the K_v current have been identified, and the K_v channels present in vascular smooth muscle have been divided into groups based on their voltage-dependence and pharmacological data. To date, more than 30 genes encoding several subfamilies of K_v α-subunits are currently recognized (Korovkina and England, 2002). Structurally, α-subunits in K_v channels have cytoplasmic N- and C- termini and contain pore-

forming six transmembrane domains (S1–S6) with an S4 voltage-sensing transmembrane domain (Korovkina and England, 2002). Each α -subunit is associated with ancillary β -subunits, which influences the characteristics of the channel (Bähring *et al.*, 2001). Many Kv channel have similar kinetics and pharmacological properties; thus, it can be difficult to determine which Kv channel genes are being expressed in a particular cell. However, it has been shown that the Kv1.5, Kv2.2, and Kv β 4 subunits are expressed in canine vascular smooth muscle cells (Horowitz, 1997), whereas the Kv1.1, Kv1.2, Kv1.4, Kv1.5, Kv1.6, Kv2.1, and Kv9.3 subunits, as well as the Kv β 1, Kv β 2, and Kv β subunits are expressed in smooth muscle cells of the pulmonary artery (Yuan *et al.*, 1998; Standen and Quayle, 1998).

The compound 4-Aminopyridine (4-AP) has been used in many studies of vascular smooth muscle as a Kv channel blocker in order to separate the Kv current from BK_{Ca} current, which is also activated by membrane depolarization (Okabe *et al.*, 1987; Smirnov and Aaronson, 1992; Nelson and Quayle, 1995). The concentration of 4-AP needed for half-maximal inhibition of Kv channels function in various types of vascular smooth muscle has been shown to be between 0.3 and 1.1 mM (Okabe *et al.*, 1987; Smirnov and Aaronson, 1992; Gelband and Hume, 1992). Though 4-AP has no effect on BK_{Ca} or Kir channels at these concentrations, inhibition of K_{ATP} currents has been reported (Beech and Bolton, 1989c; Quayle *et al.*, 1993; Nelson and Quayle, 1995). Of the various compounds known to inhibit K⁺ channel function, including Ba²⁺ (50 μ M for Kir channel), glibenclamide (10 μ M for K_{ATP} channel), and iberiotoxin (100 nM for BK_{Ca} channel), none has been shown to alter the Kv current at its working concentration (Nelson and Quayle, 1995).

Ca²⁺-activated K⁺ channels (BK_{Ca} channels)

Large-conductance (200 ~ 250 pS) Ca²⁺-activated K⁺ (BK_{Ca}) channels are a persistent feature of vascular smooth muscle cells (Fig. 1B). BK_{Ca} channels, which are activated by changes in the intracellular Ca²⁺ concentration and membrane depolarization, are believed to contribute to the maintenance of the membrane potential in small myogenic vessels (Nelson and Quayle, 1995; Waldron and Cole, 1999; Park *et al.*, 2007a). The efflux of K⁺ that results from BK_{Ca} channel activation can be used to counteract pressure- or chemical-induced depolarization and vasoconstriction (Brayden and Nelson, 1992; Tanaka *et al.*, 2004).

Similar to Kv channels, BK_{Ca} channels are comprised of a pore-forming α -subunit and a regulatory β -subunit (Knaus *et al.*, 1994; Toro *et al.*, 1998; Tanaka *et al.*, 2004). α -Subunits contain six transmembrane-spanning domains (S1–S6), including a voltage sensor (S4), which form the pore (Nelson and Quayle, 1995). However, the α -subunits, which are produced from a single gene (*slo*) by alternative splicing (McCobb *et al.*, 1995; Standen and Quayle, 1998; Waldron and Cole, 1999), contain an additional seventh transmembrane region (S0) at exoplasmic NH₂ terminus (Wallner *et al.*, 1996; Tanaka *et al.*, 2004). In addition, there are four β -subunit isoforms (β 1-4), each with two transmembrane domains, which may be associated with the α -subunits in a 1:1 ratio (Wallner *et al.*, 1995). Of the four isoforms, β 1 subunit is the predominant isoform in vascular smooth muscle (Jiang *et al.*, 1999; Tanaka *et al.*, 2004). The major function of the β -subunits is to enhance the Ca²⁺ sensitivity of the channel (Meera *et al.*, 1996; Tanaka *et al.*, 1997; Waldron and Cole, 1999).

BK_{Ca} channel may be blocked by external TEA, iberiotoxin, and charybdotoxin at half-inhibition value of 200 μ M, < 10 nM, and ~ 10 nM, respectively (Miller *et al.*, 1985; Langton *et al.*, 1991; Giangiaco *et al.*, 1992; Nelson and Quayle, 1995). Of these blockers, iberiotoxin is the most selective blocker; it has a very low half-inhibition value and its value is ineffective against the other types of K⁺ channels (Wallner *et al.*, 1995). Charybdotoxin has been used as a selective BK_{Ca} channel blocker; however, it also affects Kv channels as well as intermediate-conductance Ca²⁺-activated K⁺ channels (Carl *et al.*, 1991; Grebremedhin *et al.*, 1996; Waldron and Cole, 1999). BK_{Ca} channels are not affected by glibenclamide, Ba²⁺ or apamin, which blocks low-conductance Ca²⁺-activated K⁺ channels, at their working concentrations (Nelson and Quayle, 1995). Both NS-004 and NS-1619 have been used to stimulate BK_{Ca} channels in smooth muscle (Hu and Kim, 1996; Edwards *et al.*, 1994), but they are of limited value given their nonspecific inhibitory effects on L-type Ca²⁺ channels (Sargent *et al.*, 1993; Sheldon *et al.*, 1997; Park *et al.*, 2007b). Given this information, one should exercise caution when using these types of agents to study BK_{Ca} channels.

ATP-sensitive K⁺ channels (K_{ATP} channels)

ATP-sensitive K⁺ (K_{ATP}) channels have been first identified by in cardiac muscle and then, they have been found in various cells including vascular smooth muscle (Fig. 1C) (Noma, 1983; Nelson and Quayle, 1995). It has been shown both *in vitro* and *in vivo* that a block in K_{ATP} channels leads to vasoconstriction and membrane depolarization in various types of vascular smooth muscle (Nelson *et al.*, 1990; Nakashima and Vanhoutte, 1995, Quayle *et al.*, 1997; Teramoto, 2006). K_{ATP} channel activation is closely associated with several pathophysiological responses, including systemic arterial dilation during hypoxia (Daut *et al.*, 1990; Brayden, 2002), reactive hyperemia in coronary and cerebral circulation (Kanatsuka *et al.*, 1992; Bari *et al.*, 1998; Brayden, 2002), and acidosis- and endotoxic shock-induced vasodilation (Landry and Oliver, 1992; Ishizaka and Kuo, 1996; Kinoshita and Katusic, 1997). Moreover, the inhibition of K_{ATP} channels leads to impaired coronary and cerebral autoregulation (Narishige *et al.*, 1993; Hong *et al.*, 1994; Nelson and Quayle, 1995).

The single-channel conductances reported for K_{ATP} channels in vascular smooth muscle vary considerably; however, they clearly fall into two distinct categories: small/medium conductances and large conductances (Quayle *et al.*, 1997). Values between 7 and 15 pS have been reported for small/medium-conductance K_{ATP} channels at 6 mM [K⁺]_o, whereas values between 20 and 25 pS have been reported at 60 mM [K⁺]_o; conductances in the range of 20 ~ 50 pS have been identified at symmetric high K⁺ in arterial smooth muscle cells (Kajioka *et al.*, 1991; Beech *et al.*, 1993; Kamouchi and Kitamura, 1994; Dart and Standen, 1995; Nelson and Quayle, 1995; Zhang and Bolton, 1995; Teramoto and Brading, 1996; Quayle *et al.*, 1997). The K_{ATP} channels with larger unitary conductances between 130 and 260 pS in high K⁺ have been recorded in smooth muscle cells from aorta, renal arteriole, mesenteric artery, and rat tail artery (Standen *et al.*, 1989; Lorenz *et al.*, 1992; Furspan and Webb, 1993; Matzno *et al.*, 1995; Quayle *et al.*, 1997). The reason for the broad range of single-channel conductances among K_{ATP} is unknown; However, it indicates that channel conductance can be altered depending on the experimental conditions (e.g., the recording solution, digestive enzyme, and excised patch

configuration) and/or that multiple isoforms of the channel exist (Nelson and Quayle, 1995).

K_{ATP} channels are hetero-octameric complexes containing four pore-forming, inwardly rectifying channel subunits (Kir6.1 or Kir6.2), together with four sulphonylurea receptors (SURs), which are ATP-binding cassette (ABC) family proteins (Babenko *et al.*, 1998; Standen and Quayle, 1998; Teramoto, 2006). The molecular diversity that exists between species and tissues in terms of their K_{ATP} channel is magnified by the presence of multiple isoforms of SUR (SUR1, SUR2A, and SUR2B) (Brayden, 2002). K_{ATP} channels in vascular smooth muscle most likely contain Kir6.X/SUR2B, as co-expression of SUR2B with Kir6.1 or Kir6.2 has been shown to produce channels with the properties of native K_{ATP} channels in smooth muscle (Yamada *et al.*, 1997; Koh *et al.*, 1998; Standen and Quayle, 1998; Cui *et al.*, 2002).

K_{ATP} channels in smooth muscle are known to be inhibited by anti-diabetic sulphonylurea drugs, such as glibenclamide and tolbutamide (Fig. 1C). Glibenclamide is the most frequently used inhibitor of K_{ATP} channels in studies of arterial smooth muscle, with a half-inhibition value between 20 and 200 nM (Beech *et al.*, 1993; Xu and Lee, 1994; Nelson and Quayle, 1995; Quayle *et al.*, 1995). Tolbutamide, with a half-inhibition value of 350 μ M in smooth muscle, is considerably less effective than glibenclamide as a hypoglycemic agent (Quayle *et al.*, 1995). U-37883A and 5-hydroxydecanoate are selective inhibitors of non-vascular K_{ATP} channels with half-inhibition values of 0.26 μ M and 0.16 μ M, respectively (Notsu *et al.*, 1992; Guillemare *et al.*, 1994; Quayle *et al.*, 1997). External Ba²⁺ also could be act as an inhibitor of K_{ATP} channels in smooth muscle, with a half-inhibition value of 100 μ M at -80 mV (Nelson and Quayle, 1995; Quayle *et al.*, 1988; Bonev and Nelson, 1993). The K_{ATP} channels are not affected by iberitoxin and are less sensitive to TEA, with a half-inhibition value of 7 mM in both smooth and skeletal muscle (Davies *et al.*, 1989; Nelson and Quayle, 1995; Quayle *et al.*, 1995). Numerous synthetic K⁺ channel activators belonging to several distinct classes have been produced, including cromakalim, levcromakalim, nicorandil, pinacidil, minoxidil, diazoxide, and BRL-55834 (Quayle *et al.*, 1997). The vasodilation induced by these agents can be successfully blocked by glibenclamide; thus, they are believed to hyperpolarize the cells in vascular smooth muscle by targeting K_{ATP} channels. However, other K⁺ channel blockers, such as iberitoxin, apamin, or low concentrations of TEA are ineffective to K_{ATP} channels (Brayden, 2002).

Inward rectifier K⁺ channels (Kir channels)

Inward rectifier K⁺ (Kir) channels are abundant in the smooth muscle of small-diameter resistance vessels (Fig. 1D) (Knot *et al.*, 1996; Quayle *et al.*, 1996; Park *et al.*, 2006a). Though the exact function of Kir channels in vascular smooth muscle is still incomplete, there are two basic possibilities. First, Kir channels contribute to the resting membrane potential and resting tone in small-diameter vascular smooth muscle. This hypothesis is supported by studies showing the constriction of small-diameter coronary and cerebral arteries at resting tone in response to Ba²⁺, a specific inhibitor of Kir channels (Park *et al.*, 2007c, Park *et al.*, 2007d). Second, Kir channel activation in response to moderate increases in the extracellular K⁺ concentration (to 10–15 mM) may cause vasodilation. Evidence for this hypothesis comes from the fact that vasodilation can be prevented by Ba²⁺ but not by removal of the endothelium or by inhibitors of the other K⁺ channels (Nelson and Quayle, 1995; Knot *et al.*, 1996; Chrissobolis *et*

al., 2000; Zaritsky *et al.*, 2000; Eckman and Nelson, 2001; Rivers *et al.*, 2001; Park *et al.*, 2007d).

The Kir channels in vascular smooth muscle cells mediate inward currents at membrane potentials that are negative relative to the E_K and small outward currents at membrane potentials that are positive relative to the E_K (Edwards and Hirst, 1988; Edwards *et al.*, 1988; Quayle *et al.*, 1993). Given that the membrane potential of vascular smooth muscle is normally positive relative to the E_K , a physiological role for the inward rectifier channel requires outward current through the channel (Robertson *et al.*, 1996). The measured outward current is on the order of a few picoamperes, possibly as a result of internal Mg^{2+} or internal polyamine blocking (Matsuda *et al.*, 1987, Nichols *et al.*, 1996; Xu *et al.*, 1999). Only a few papers have addressed the single-channel properties of Kir channel in vascular smooth muscle. The first report of single channel currents corresponding to Kir (Kir2.1) channel, a 21 pS single-channel conductance in small-diameter coronary arteries, was made by our group (Park *et al.*, 2005c). Similarly, a conductance of 20 pS has been reported for Kir2.1 channels in human pulmonary artery smooth muscle cells (Tennant *et al.*, 2006). However, additional studies are required to produce a more detailed picture of the single channel conductance of Kir channels in vascular smooth muscle cells.

Kir channels are tetramers whose subunits, each of which contains only two transmembrane domains, are encoded by members of the *Kir* gene family (Standen and Quayle, 1998; Kubo *et al.*, 2005). Channels formed from subunits encoded by the Kir2.0 gene subfamily exhibit properties that are typical of native strong inward rectifiers. Moreover, their biophysical properties in coronary, cerebral, basilar arterial smooth muscle correspond closely to those reported for Kir2.1 channels expressed in a heterologous system, suggesting that Kir2.1, but not Kir2.2 or Kir2.3, is expressed in vascular smooth muscle (Standen and Quayle, 1998; Bradley *et al.*, 1999; Chrissobolis *et al.*, 2000; Park *et al.*, 2005c). Furthermore, targeted gene disruption of Kir2.1 (Kir2.1^{-/-}) completely abrogated the Kir currents, and arteries from Kir2.1^{-/-} animals did not dilate in response to elevated K^+ to 15 mM (Zaritsky *et al.*, 2000). However, Wu *et al.* (2007) suggested that the Kir channels in cerebral arteries contain both Kir2.1 and Kir2.2. In addition, Kir2.1 and Kir2.4 expression has been detected in cultured human pulmonary arterial smooth muscle cells (Tennant *et al.*, 2006). Additional studies are required to characterize the expression and function of each Kir subtypes.

Ba^{2+} blocks the Kir currents in vascular smooth muscle cells in a voltage-dependent fashion. In fact, the half-inhibition values for the inhibition mediated by Ba^{2+} , which has been shown to be 2.1 μM and 2.2 μM at -60 mV in coronary and cerebral arteries, respectively, increases exponentially with hyperpolarization (Quayle *et al.*, 1993; Robertson *et al.*, 1996). However, Ba^{2+} is much less effective against K_{ATP} channels (K_d , 200 μM at -60 mV), BK_{Ca} channels ($K_d > 10$ mM), and Kv channels ($K_d > 1$ mM) (Nelson and Quayle, 1995; Robertson *et al.*, 1996). Therefore, at concentrations below 50 μM , Ba^{2+} is a selective blocker of Kir channels in vascular smooth muscle. Cs^+ , which acts from outside the cell, also inhibits Kir currents in vascular smooth muscle with a K_d of 2.9 mM at -60 mV (Robertson *et al.*, 1996; Quayle *et al.*, 1997). External Ca^{2+} and Mg^{2+} partially block Kir channels. For example, at -60 mV, 5 mM Ca^{2+} or Mg^{2+} reduced the Kir current by 47% and 41%, respectively, (Robertson *et al.*, 1996).

Regulation of K⁺ channels

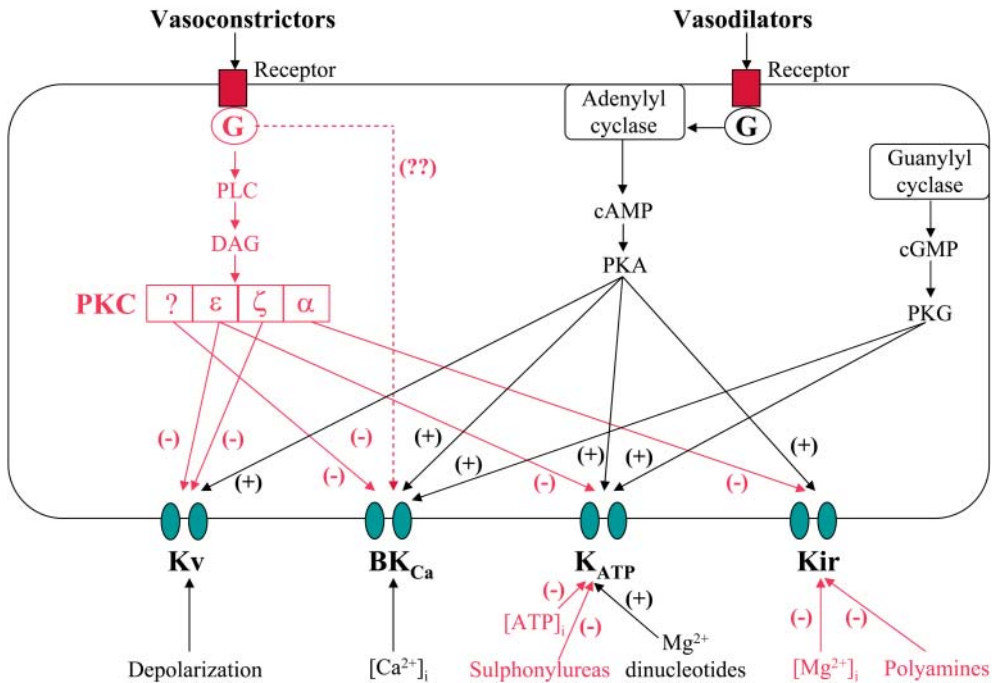


Fig. 2. Possible modulatory pathways of K⁺ channels in vascular smooth muscle cells. PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C; PKA, protein kinase A; PKG, protein kinase G.

Modulation of K⁺ channels by vasoactive substances

Effect of vasoconstrictors on K⁺ channels: role of PKC

A number of vasoconstrictors inhibit K⁺ channel activity, which contributes to membrane depolarization. Generally, vasoconstriction is initiated at membrane receptors that are coupled through a GTP-binding protein (G_q) to phospholipases, which generate the second messengers diacylglycerol and inositol 1,4,5-triphosphate (IP₃), which activate protein kinase C (PKC) (Fig. 2) (Standen and Quayle, 1998). Several PKC isoforms, including α, β, ε and ζ have been identified in vascular smooth muscle according to their Ca²⁺-dependence (Dixon *et al.*, 1994; Lee and Severson, 1994). Classic PKCs (α and β) activation requires Ca²⁺, diacylglycerol, and phosphatidylserine; in comparison, the novel PKC (ε) requires diacylglycerol and phosphatidylserine, but not Ca²⁺, and the atypical PKC (ζ) is activated by phosphatidylserine alone (Park *et al.*, 2006b).

Endothelin and angiotensin have shown to inhibit K_v currents via Ca²⁺-independent PKCε activation (Clement-Chomienne *et al.*, 1996; Shimoda *et al.*, 1998; Hayabuchi *et al.*, 2001a). More recently, K_v channel inhibition by thromboxane A₂ reportedly involves PKCζ (Cogolludo *et al.*, 2003; Crozatier, 2006). Despite the PKC-independent inhibition of BK_{Ca} channels by

angiotensin in coronary arteries (Toro *et al.*, 1990; Minami *et al.*, 1995), most recent data indicate that PKC phosphorylation inhibits BK_{Ca} channels in vascular smooth muscle (Crozatier, 2006; Ledoux *et al.*, 2006). However, the precise role of each PKC isoform remains to be determined. In vascular smooth muscle, several vasoconstrictors such as angiotensin, endothelin, vasopressin, noradrenaline, histamine, serotonin, and neuropeptide Y inhibit K_{ATP} channels function via PKC activation (primarily Ca²⁺-independent PKC ϵ) (Wakatsuki *et al.*, 1992; Bonev and Nelson, 1996; Tanaka *et al.*, 1997; Hayabuchi *et al.*, 2001b; Park *et al.*, 2005d). The inhibitory effect of these compounds on Kir channels has not been examined as extensive as their effects on other K⁺ channels. Recent papers have shown that endothelin and angiotensin have been shown to inhibit Kir channel function; however, this inhibition is closely associated with Ca²⁺-dependent PKC α activation (Park *et al.*, 2005c, 2006b). Consistent with these findings, it has been suggested that microvessels, have Kir channels, express relatively high levels of PKC α and low levels of PKC ϵ (Collins *et al.*, 1992; Dessy *et al.*, 2000).

Effect of vasodilators on K⁺ channels: role of PKA and PKG

A number of vasodilators including calcitonin gene-related peptide, β -adrenergic agonists, vasoactive intestinal peptide, and adenosine, activate adenylyl cyclase, thereby increasing the intracellular concentration of cAMP, which activates cAMP-dependent protein kinase (PKA) (Standen and Quayle, 1998). Several types of vascular K⁺ channels are activated in this mechanism (Fig. 2). The K_{ATP} channels in vascular smooth muscle are responsive to many of the vasodilators that function through PKA, including calcitonin gene-related peptide, adenosine, and isoprenaline (Kleppisch and Nelson, 1995; Quayle *et al.*, 1997; Wellman *et al.*, 1998). BK_{Ca} channels are also activated by vasodilators coupled to PKA. However, most studies have addressed activation by the β -adrenoceptor (Sadoshima *et al.*, 1988; Song and Simard, 1995; Standen and Quayle, 1998). Though the regulation of Kv channels by vasodilators has been largely ignored, β -adrenoceptor stimulation has been shown to activate Kv currents through PKA in rabbit vascular smooth muscle cells (Aiello *et al.*, 1995; Standen and Quayle, 1998). More recently, it was suggested that the potent vasodilator, adenosine also activates Kir currents through PKA (Park *et al.*, 2005e; Son *et al.*, 2005). Kir channels, like other K⁺ channels, may also be modulated by other important vasodilators; additional studies are required to solve this issue.

Some vasodilators act through guanylyl cyclase, leading first to an increase in intracellular cGMP, then consequently activates cGMP-dependent protein kinase (PKG) (Standen and Quayle, 1998). The activation of PKG by nitric oxide or nitrovasodilators results in the activation of BK_{Ca} channels in isolated smooth muscle cells from coronary and cerebral arteries (Williams *et al.*, 1988; Robertson *et al.*, 1993). There is also some evidence that PKG can activate the K_{ATP} channels in certain types of vascular smooth muscle. Atrial natriuretic factor and isosorbide dinitrate increase the intracellular cGMP level in cultured vascular smooth muscle cells, leading to the activation of individual K_{ATP} channels (Miyoshi *et al.*, 1994; Kubo *et al.*, 1994; Nelson and Quayle, 1995). Furthermore, nitric oxide induces glibenclamide-sensitive K⁺ current in vascular smooth muscle, suggesting that either a rise in the level of cGMP or stimulation of PKG leads to K_{ATP} channel activation (Fig. 2) (Murphy and Brayden, 1995; Nelson and Quayle, 1995).

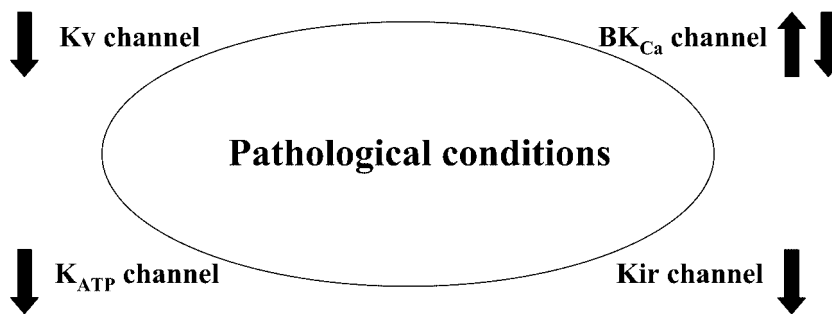


Fig. 3. Pathological alteration of K^+ channels in vascular smooth muscle cells.

Alteration of K^+ channels in pathological conditions

Impaired K^+ channel function in vascular smooth muscle cells has been detected in various pathological conditions including hypertension, diabetes, ischemia/reperfusion, and brain injury (Fig. 3). For Kv channels, several studies have reported reduced Kv channel function in hypertension and hypertrophy (Martens and Gelband, 1996; Kim *et al.*, 2001; Wellman *et al.*, 2001). Pathological alterations of K_{ATP} channels are relatively well characterized in diabetes, ischemia, and hypertension; these studies clearly demonstrated impaired K_{ATP} channel function and altered gene expression in various arteries (e.g., Mayhan, 1994; Bari *et al.*, 1996; Ghosh *et al.*, 2004). In spite of the fact that BK_{Ca} channel function is believed to be enhanced by such pathological conditions as hypertension (Liu *et al.*, 1998), some reports suggest that BK_{Ca} channel function is reportedly diminished in hypertrophy, (Kim *et al.*, 2003) or is unaffected by ischemia (Bari *et al.*, 1997). Recent evidence suggests that Kir channels are also affected by hypertension, ischemia, hypertrophy, and diabetes (McCarron and Halpern, 1990; Marrelli *et al.*, 1998; Mayhan *et al.*, 2004; Park *et al.*, 2007c), but additional studies are necessary to establish a mechanism.

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