Minireview

Role of potassium channels in coronary vasodilation

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Abstract

K^+ channels in coronary arterial smooth muscle cells (CASMC) determine the resting membrane potential (E_m) and serve as targets of endogenous and therapeutic vasodilators. E_m in CASMC is in the voltage range for activation of L-type Ca^{2+} channels; therefore, when K^+ channel activity changes, Ca^{2+} influx and arterial tone change. This is why both Ca^{2+} channel blockers and K^+ channel openers have such profound effects on coronary blood flow; the former directly inhibits Ca^{2+} influx through L-type Ca^{2+} channels, while the latter indirectly inhibits Ca^{2+} influx by hyperpolarizing E_m and reducing Ca^{2+} channel activity. K^+ channels in CASMC play important roles in vasodilation to endothelial, ischemic and metabolic stimuli. The purpose of this article is to review the types of K^+ channels expressed in CASMC, discuss the regulation of their activity by physiological mechanisms and examine impairments related to cardiovascular disease.

Keywords: coronary blood flow, coronary vascular smooth muscle, large conductance Ca^{2+}- and voltage-activated K^+ channel, ATP-dependent K^+ channel, voltage-gated K^+ channel

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Ca^{2+} channels, K^+ channels and coronary blood flow

K^+ channels dominate the membrane conductance of coronary arterial smooth muscle cells (CASMC) at rest and thus determine E_m (Figure 1). That is, E_m is closer to the Nernst equilibrium potential for K^+ (E_K) than for other ions. E_K in arterial smooth muscle is estimated to be -83 mV.[1] An asymmetric distribution of K^+ across the cell membrane is maintained by the Na^+/K^+-ATPase and provides a large chemical driving force for K^+ efflux by diffusion through open channels. If K^+-selective channels were the only type of channels open in CASMC at rest, K^+ would diffuse out of the cell until an electrical potential of -83 mV is developed. E_m in CASMC, however, is not as negative as E_K; generally, values around -50 mV are observed.[2–7] This less negative value of E_m, compared with E_K, in CASMC is because other ion channels are open at rest (e.g. those permeable to ions with more positive reversal potentials, such as Na^+ and Ca^{2+}).

Balancing the hyperpolarizing influence of K^+ channels with the depolarizing influence of other channels produces a stable E_m in CASMC typically between -60 and -40 mV. The voltage threshold for L-type Ca^{2+} current activation, and thus contraction, is in this range.[3,6,8,9] CASMC are generally electrically quiescent, respond to stimuli with graded potentials and do not normally display action potentials. However, if K^+ channels are inhibited with tetraethylammonium (TEA; a non-selective blocker of K^+ channels), Ca^{2+}-dependent action potentials can be observed.[10–12] L-type Ca^{2+} channel inhibitors and K^+ channel openers inhibit phasic contractions induced by TEA and 4-aminopyridine (4-AP; an inhibitor of voltage-dependent K^+, K_V channels[5,12–16]). Such findings have led to the hypothesis that coronary vasospasm may be related to reduced K^+ conductance in CASMC.[17]

Multiple types of K^+ channels are expressed in CASMC, but it seems that some have more important roles in determining E_m and the state of contraction under resting conditions. For example, 4-AP strongly contracts conduit coronary arteries,[15,18] whereas charybdotoxin, iberiotoxin, apamin and glibenclamide cause little or no contraction.[15] Charybdotoxin and iberiotoxin inhibit large conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels, apamin inhibits some small conductance Ca^{2+}-activated K^+ channels and glibenclamide inhibits ATP-dependent K^+ (K_{ATP}) channels. There may be complex heterogeneity in ion channel expression and function throughout the coronary tree;

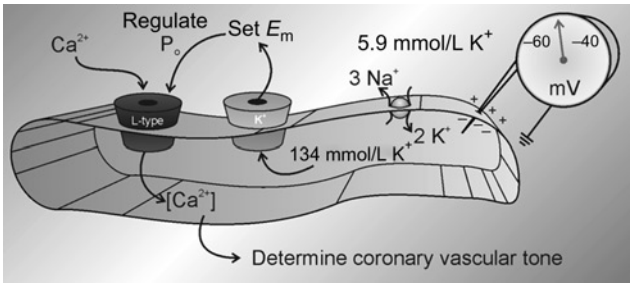

Figure 1 Electromechanical coupling in CASMC. The Na^+/K^+-ATPase accumulates intracellular K^+, providing a large chemical gradient for diffusion of K^+ through open channels. Efflux of K^+ largely determines E_m, which regulates the open probability of L-type Ca^{2+} channels. The level of free intracellular Ca^{2+} determines the contractile state of coronary vascular smooth muscle. CASMC, coronary arterial smooth muscle cells

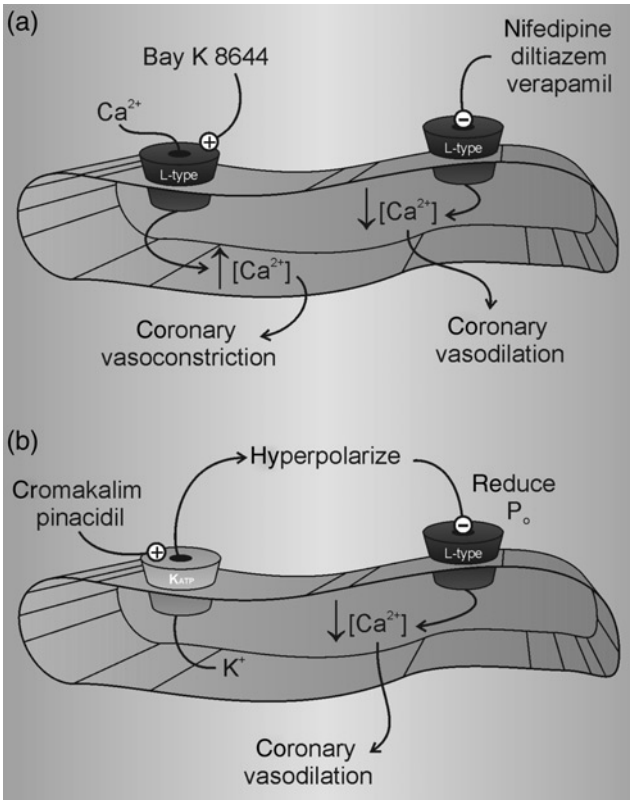

Figure 2 K^+ channel openers and Ca^{2+} channel blockers. (a) Drugs that modulate L-type Ca^{2+} channel activity affect coronary vascular tone. Nifedipine, diltiazem and verapamil reduce intracellular Ca^{2+} and lead to vasodilation. In contrast, Bay K 8644 increases intracellular Ca^{2+} and leads to vasoconstriction. (b) K^+ channel openers, e.g. K_{ATP} channel agonists pinacidil and cromakalim, hyperpolarize E_m. This reduces the open probability of L-type Ca^{2+} channels, lowers the free intracellular Ca^{2+} concentration and produces vasodilation. The K_{ATP} channel antagonist glibenclamide has an opposite effect

while glibenclamide does not contract conduit coronary arteries, it does tend to diminish the balance between coronary blood flow and myocardial metabolism, indicating increased microvascular resistance.[19–22] BK_{Ca}, K_V and K_{ATP} channels have important roles in certain facets of coronary vascular regulation; therefore, the properties of these channels and the modulation of their activity are discussed in the next section.

Antagonists of L-type Ca^{2+} channels such as nifedipine, verapamil and diltiazem increase coronary blood flow,[23–26] as these drugs relax coronary arteries and arterioles.[27–30] Conversely, Bay K 8644, a dihydropyridine with agonist rather than antagonist properties, elicits coronary vasoconstriction.[31] The coronary vasodilator effects of L-type Ca^{2+} channel blockers are rather simple to understand; these drugs directly inhibit a major Ca^{2+} entry pathway in CASMC and thus reduce the intracellular Ca^{2+} required to maintain contraction. The vasodilatory effects of K^+ channel openers are similar; however, their mechanism involves an additional step to hyperpolarize E_m. Pinacidil and cromakalim, two K^+ channel openers, increase coronary blood flow.[32–34] These agents relax coronary smooth muscle by activating K_{ATP} channels.[35–38] In doing so, these drugs render E_m more negative and reduce the open probability of L-type Ca^{2+} channels in CASMC,[8,9] thus limiting Ca^{2+} influx and promoting vasodilation. This interplay between K^+ channels and voltage-dependent Ca^{2+} channels in CASMC represents a reasonably straightforward example of electromechanical coupling (Figure 2).

CASMC, of course, express a wide variety of cation and anion channels with important functions that extend far beyond electromechanical coupling (e.g. references[39–44]); however, this review focuses on just a few of the types of K^+ channels involved in coronary vasodilation. While only BK_{Ca}, K_V and K_{ATP} channels are discussed, it is clear that other K^+ channels are expressed in CASMC and play important roles (e.g. additional types of Ca^{2+}-activated K^+ channels and inwardly rectifying K^+ channels[45–47]). Additionally, it is clear that the ion channels of other cells in the coronary vascular wall function to regulate microcirculatory tone (e.g. K_{ATP} channels in endothelial cells regulate NO release;[48,49]); however, our discussion will be limited to K^+ channels in CASMC.

Types of K^+ channels expressed in CASMC

The K^+ currents and the electrophysiological properties of CASMC have been demonstrated using patch clamp techniques (e.g. by Wilde and Lee[50] in dog coronary artery). CASMC E_m was −51 mV and the current was TEA-sensitive, K^+-selective and abolished by intracellular Cs^+. Input resistance was very high ($>10^8$ Ohms); therefore, small changes in current produce large changes in E_m. K^+ current increased with elevations in extracellular or intracellular Ca^{2+}, indicating the functional expression of K_{Ca} channels. Total whole-cell K^+ current consisted of at least two components based on amplitude, time dependence, sensitivity to Ca^{2+} and pharmacology. Specifically, there was a fast activating current followed by a larger and slower current; the fast component was more sensitive to block by extracellular Cs^+, whereas the slow component was more sensitive to block by TEA. The slower component was increased by elevations in intracellular or extracellular Ca^{2+}, but the fast component was little affected. Other patch clamp studies of rabbit and human CASMC elaborated on these two major types of K^+ currents (established to be BK_{Ca} and K_V) and demonstrated a predominance of K_V current in the physiological range of E_m.[51–54] BK_{Ca} channels activate at more depolarized potentials than K_V

channels in CASMC[52] but increases in intracellular Ca^{2+} open BK_{Ca} channels at physiologically relevant voltages.[55,56] Activating Ca^{2+} for BK_{Ca} channels in CASMC comes from spontaneous release from intracellular stores,[56] L-type Ca^{2+} channels[57] and receptor stimulation.[58,59]

The first patch clamp studies of CASMC K^+ channels did not reveal notable K_{ATP} channel activity, but this is largely due to the use of conventional dialyzed patch techniques that included mmol/L concentrations of intracellular ATP and effectively inhibited K_{ATP} channels. Dart and Standen,[60,61] however, used nystatin- and amphotericin-perforated patch techniques (where the intracellular ATP concentration was not artificially manipulated) to demonstrate adenosine- and hypoxia-activated K_{ATP} current in CASMC. Pinacidil activates K_{ATP} currents in human CASMC regardless of the intracellular ATP concentration.[38,52] The discussion below concerns the molecular composition and regulation of BK_{Ca}, K_{ATP} and K_V in CASMC (Figure 3).

BK_{Ca} channels in CASMC

BK_{Ca} channels are large conductance (>200 pS), voltage-sensitive K^+ channels regulated by Ca^{2+} in an allosteric fashion.[62] The assembly of four pore-forming α subunits, products of single alternatively spliced gene (KCNMA1), can form functional BK_{Ca} channels. Studies have identified four types of modulatory β subunits. The accessory $\beta1$ subunit (KCNMB1) increases sensitivity to Ca^{2+}, slows activation and deactivation, and reduces sensitivity to iberiotoxin.[63] In human CASMC, the majority of BK_{Ca} channels contain this $\beta1$ subunit.[64] Multiple stimuli regulate BK_{Ca} channel activity. As can be surmised from the previous section, those coupling to coronary vasoconstriction typically inhibit BK_{Ca} channels, while those coupling to coronary vasodilation typically activate BK_{Ca} channels.

BK_{Ca} channels are involved in CASMC responses to endothelial stimulation. The coronary vascular endothelium produces a number of relaxing factors such as nitric oxide (NO), prostacyclin (PGI_2) and epoxyeicosatrienoic acids (EETs). While the term endothelium-derived hyperpolarizing factor (EDHF) is typically reserved for the mediator(s) of dilations remaining after inhibition of NO synthase and cyclooxygenase, the term EDHF should be applied to any endothelium-derived factor that activates K^+ channels. That is, one can consider NO an EDHF, as it activates BK_{Ca} channels in CASMC.[65–68] S-nitrosothiols have similar effects on BK_{Ca} channels in CASMC, and the actions of both NO and S-nitrosothiols appear to involve cyclic guanosine monophosphate (cGMP) signaling.[68–70] Some metabolites of arachidonic acid produced by cyclooxygenase, such as PGE_2, activate BK_{Ca} channels through cAMP and cross-activation of the cGMP-signaling pathway.[71,72] Various metabolites of arachidonic acid produced by other enzyme systems, such as EETs from cytochrome P450 metabolism, activate BK_{Ca} channels in CASMC.[73–77]

The mediators of ischemic and metabolic vasodilation in the coronary circulation have not been identified conclusively;[78,79] however, K^+ channels appear to be end-effectors and several putative dilator mechanisms have been examined. Sympathetic stimulation plays an important role in coronary metabolic vasodilation[80,81] and the β-adrenergic agonist isoproterenol activates BK_{Ca} channels in CASMC.[72,82] This appears to be mediated by $G_s\alpha$ and cross-activation of cGMP-dependent protein kinase; dopamine has similar effects.[72,83] Adenosine is proposed as a mediator of ischemic and metabolic vasodilation; however, no patch clamp data show a stimulatory effect of adenosine on BK_{Ca} channels in CASMC (such data are available in mesenteric smooth muscle[84]). H_2O_2, a putative metabolic vasodilator, activates BK_{Ca} channels in CASMC;[85] this may be

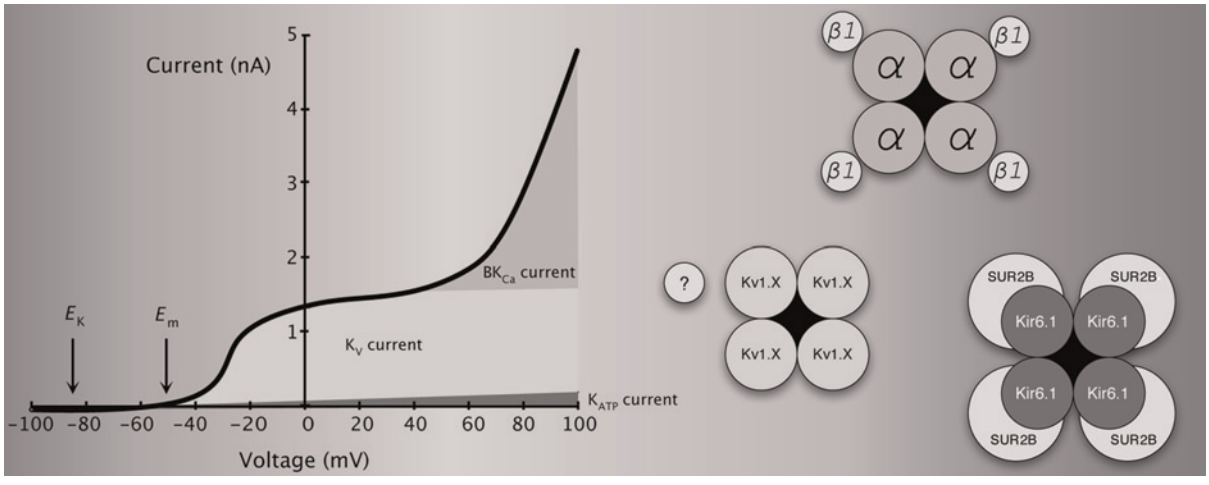

Figure 3 Macroscopic K^+ currents in CASMC and molecular composition of the channels responsible. K_V and BK_{Ca} channels mediate the two most prominent currents, although K_{ATP} channels are also expressed. Functional BK_{Ca} channels can be formed by the assembly of four pore-forming α subunits, which contain regulatory regions responding to voltage and Ca^{2+}. In CASMC, most BK_{Ca} channels are complimented by four accessory $\beta1$ subunits, which increase Ca^{2+}/voltage sensitivity and alter biophysical and pharmacological properties. K_{ATP} channels are an octameric complex of four pore-forming α subunits and four regulatory sulfonylurea receptors (SUR). The likely K_{ATP} subunits in CASMC are Kir6.1 and SUR2B. Functional K_V channels are formed by the assembly of four pore-forming α subunits, which are sensitive to voltage. The addition of auxiliary or modifying subunits can change channel properties. The identity of K_V channel subunits in CASMC remains an active area of investigation; however, a major portion of the current is sensitive to correolide, indicative of K_V1 expression. CASMC, coronary arterial smooth muscle cells

mediated by activation of phospholipase A_2 and production of lipoxygenase metabolites.[86]

A variety of substances that constrict coronary vessels inhibit BK_{Ca} channels. Angiotensin II,[87,88] endothelin-1[87,89] and thromboxane A_2[90] inhibit BK_{Ca} channels in CASMC. Common underlying mechanisms for inhibition of BK_{Ca} by these G protein-coupled receptors may include activation of protein kinase C[91] or c-Src, a tyrosine kinase.[92]

K_{ATP} channels in CASMC

Functional K_{ATP} channels are composed of eight subunits: four pore-forming subunits (either Kir6.1 or Kir6.2) and four sulfonylurea receptors (SUR1, SUR2A or SUR2B; the 2A and 2B isoforms are splice variants of the same gene, ABCC9). *In situ* hybridization and RT-PCR show Kir6.1 and SUR2B mRNA in coronary arteries and arterioles[93,94] and immunohistochemistry indicates Kir6.1 and SUR2 proteins in coronary arterioles $<100\ \mu$m.[94,95] Kir6.1-null mice demonstrate coronary vasospasm,[96] but Kir6.2-null mice do not.[97] Genetic ablation of ABCC9 (encoding both SUR2A and SUR2B) also produces coronary vasospasm.[98] These studies support the idea that CASMC K_{ATP} channels are composed of Kir6.1 and SUR2A/B subunits, as knockout of these subunits produce coronary vasospasm. The mechanism may be much more complex, however, as smooth muscle-specific restoration of SUR2 expression in knockout mice does not correct coronary vasospasm.[99] Thus, coronary vasospasm in Kir6.1 and SUR2A/B mice may be secondary to some other change and unrelated to channels in CASMC.

K_{ATP} channels in CASMC may be the targets of endothelium-dependent relaxing factors, but there are few patch clamp studies to provide direct evidence. For example, no patch clamp study has demonstrated the activation of K_{ATP} channels by NO in CASMC (such data are available in bladder smooth muscle[100]). With regard to ischemic vasodilation, it has been demonstrated that adenosine and hypoxia activate K_{ATP} channels in CASMC.[60,61] In the context of metabolic vasodilation, dopamine, an endogenous catecholamine, has been shown to activate K_{ATP} in CASMC.[101] In contrast, coronary vasoconstrictors including endothelin-1, vasopressin and angiotensin II inhibit K_{ATP} channels.[102–104]

K_V channels in CASMC

More than 40 K_V channel subunits have been identified; because of this diversity, the molecular identity of K_V channels in CASMC remains unclear. Complexity arises not only from the sheer number of genes involved, but is compounded by the alternative splicing of mRNA encoding individual subunits, assembly of different subunits into heteromultimeric channels and a variety of post-translational modifications. Functional K_V channels are a tetrameric assembly of pore-forming α subunits, but multiple types of accessory subunits modify K_V channel properties. The K_V current in CASMC is a delayed rectifier with little or no time-dependent inactivation. Its biophysical behaviors share many properties with some channels cloned from the K_V1 (Shaker; KCNA), K_V2 (Shab; KCNB) and K_V3 (Shal; KCNC) gene families. Sections of the human heart demonstrate $K_V1.5$ immunoreactivity in CASMC.[105] Further, K_V1 family genes, multiple K_V1 proteins and current sensitive to correolide (a blocker of Shaker-type K_V1 channels) are expressed in canine and rat coronary artery.[106,107] K_V3 gene transcripts and a highly TEA-sensitive K_V current are expressed in pig coronary arteries.[108] More studies will be required to determine the molecular composition of delayed rectifier channels in CASMC, as well as differences that may be due to species, vessel caliber and other factors (e.g. side of the heart from which the vessels originate[107]).

NO and iloprost (a PGI_2 mimetic), but not 11,12-EET (an EDHF from the cytochrome P450 pathway), activate K_V channels in CASMC.[67] No patch clamp study demonstrates effects of adenosine or β-adrenergic agonists on K_V current in CASMC; however, a common signaling pathway may be cAMP-dependent protein kinase, which has been shown to activate K_V channels in portal vein smooth muscle.[109,110] H_2O_2, a putative metabolic vasodilator, activates K_V channels in CASMC through unknown signaling mechanisms.[111] No patch clamp studies demonstrate inhibition of K_V channels by vasoconstrictors in CASMC; however, data are available from other vascular beds. Endothelin-1, angiotensin II and thromboxane A_2 inhibit K_V current in the mesenteric artery, pulmonary artery and portal vein smooth muscle and a common mechanism appears to be activation of protein kinase C.[112–115] In cerebral arterial smooth muscle, Rho kinase and tyrosine kinases, involved in CASMC Ca^{2+} regulation and contraction, inhibit K_V current.[116,117]

Regulation of CASMC K^+ channels by endogenous vasodilators

Many mechanisms regulate coronary vascular resistance,[79,118,119] several of which were introduced in the above section. Factors from the endothelium influence coronary vascular tone, ischemia is an important pathophysiological stimulus and metabolism is the key regulator of coronary blood flow on a beat-to-beat basis. Importantly, K^+ channels play a central role in producing vasodilation to all of these stimuli and their endogenous mediators. At present, the study of K^+ channels in coronary blood flow depends almost entirely upon pharmacological blockers (e.g. iberiotoxin, glibenclamide and 4-AP) and very few investigators have been able to take advantage of newer, and perhaps more specific, molecular tools. Hopefully, models that incorporate knockout, transgenic and RNA interference approaches will receive more attention in the future. The following section summarizes studies of K^+ channels in coronary vascular relaxation (*in vitro* studies of arteries and arterioles) and the regulation of coronary blood flow (*in vivo*). For simplicity, the role of K^+ channels in various coronary vascular responses are discussed one at a time; however, it is important to recognize that key vasoregulatory factors modulate coronary microvascular tone via multiple K^+ channels subtypes. For example, coronary endothelial-dependent dilation to bradykinin is mediated, to varying degrees, by BK_{Ca}, K_{ATP} and K_v channels (Figure 4a). Another example

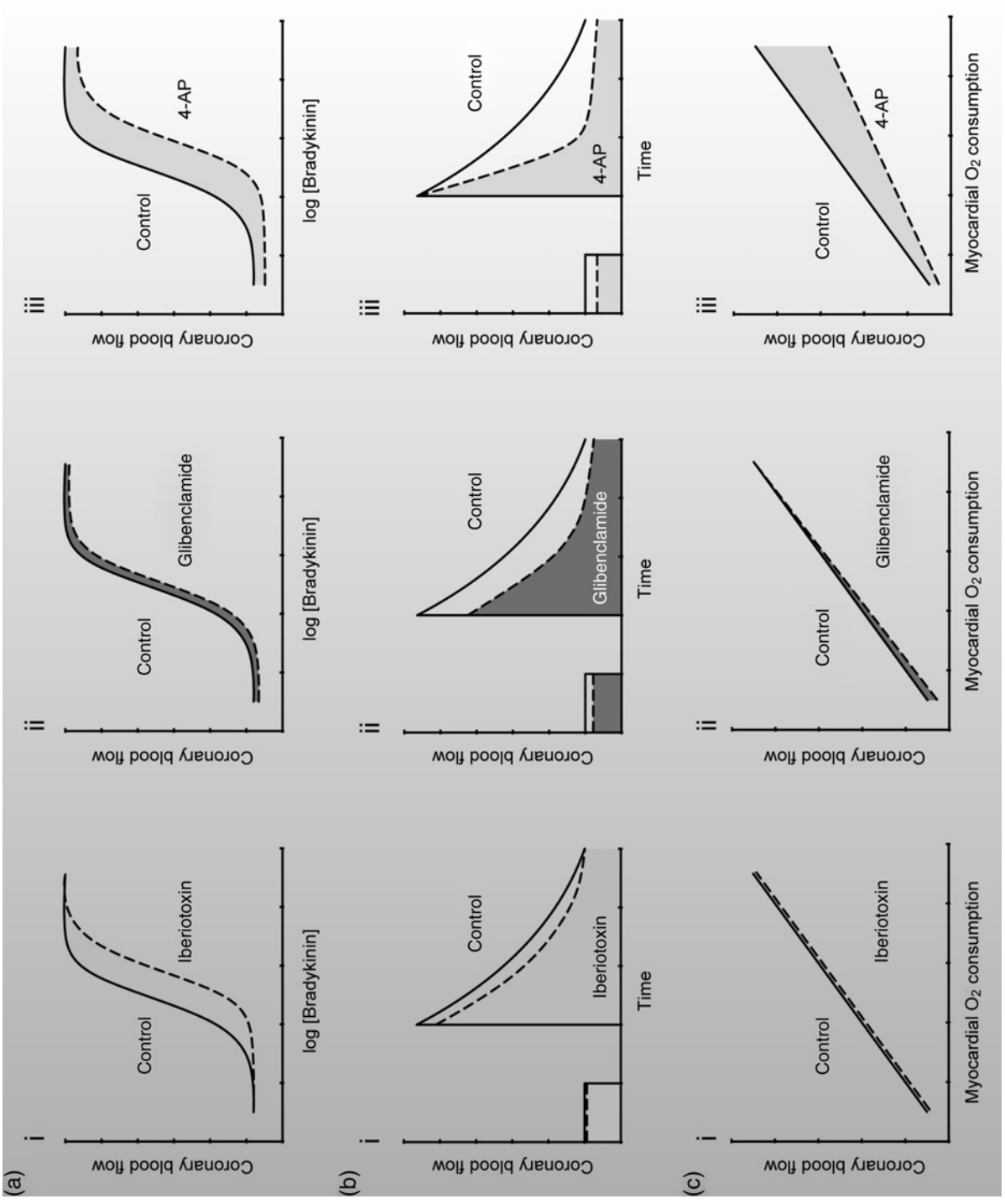

Figure 4 K^+ channels in the regulation of coronary blood flow. (a) Effects of iberiotoxin (i), glibenclamide (ii) and 4-AP (iii) on endothelium-dependent coronary vasodilation. (b) Roles of BK_{Ca} (i), K_{ATP} (ii) and K_V (iii) channels in coronary reactive hyperemia. (c) Coronary metabolic vasodilation does not involve BK_{Ca} (i) or K_{ATP} (ii) channels, but does depend upon the opening of K_V channels (iii). 4-AP, 4-aminopyridine

is how ischemic coronary vasodilation involves both K_{ATP} and K_v channels (Figure 4b). Dilators appear to regulate coronary blood flow through mechanisms involving multiple types of K^+ channels; therefore, if one K^+ channel type is inhibited/impaired, another may compensate. Such redundancy may act to preserve myocardial perfusion.[120] The precise roles of redundant K^+ channel pathways and signaling cross-talk in the overall control of coronary blood flow merit further investigation.

Endothelium-dependent vasodilation

Agonists such as acetylcholine and bradykinin couple to NO, PGI_2 and EDHF production and thus coronary vasodilation. Many other endothelium-dependent agonists have been tested and adenosine-induced coronary dilation also has an endothelial component.[48,49] The contribution of specific K^+ channel types to endothelium-dependent coronary vasodilation has been studied in numerous species. Iberiotoxin, a selective BK_{Ca} channel antagonist, inhibits bradykinin-induced coronary vasodilation in dogs *in vivo*.[121] Similarly, charybdotoxin, a BK_{Ca} channel antagonist, inhibits bradykinin-induced vasodilation of human coronary arterioles.[122] Iberiotoxin attenuates NO- and cGMP-induced relaxation of human[66] and animal[123–125] coronary arteries, indicating a role for BK_{Ca} channels in endothelium-dependent NO-induced hyperpolarization.[126] The role of BK_{Ca} channels in PGI_2-induced coronary artery relaxation may depend on species, as iberiotoxin inhibits hyperpolarization induced by iloprost, a stable PGI_2 mimetic, in porcine CASMC,[127] but iloprost has no effect on BK_{Ca} channels in bovine CASMC.[67] No *in vivo* study has addressed the role of BK_{Ca} channels in iloprost-induced coronary vasodilation. When NO and PGI_2 production are blocked, the remaining relaxation is attributed to EDHF (which may be a cytochrome P450 metabolite). Iberiotoxin inhibits EDHF-induced coronary relaxation *in vitro* in pigs[128] and EDHF-induced coronary vasodilation *in vivo* in dogs.[129] Some investigators present data indicating no significant role for BK_{Ca} channels in endothelium-dependent relaxation of the coronary arteries of guinea pigs,[130] dogs and monkeys,[131] as well as humans.[132] However, the general consensus seems to be that BK_{Ca} channels play at least some role in endothelium-dependent coronary vasodilation (Figure 4ai).

It is generally reported that there is no effect of glibenclamide on endothelium-dependent vasodilation to bradykinin or acetylcholine in the coronary circulation, suggesting no role for K_{ATP} channels in this response. Negative findings for glibenclamide in endothelium-dependent vasodilation have been found for coronary blood flow *in vivo*[19,133–135] and for isolated hearts and arterioles *in vitro*.[122,136] Also, glibenclamide does not affect the coronary vascular smooth muscle response to NO donors.[20] However, K_{ATP} channels have been reported as mediators of bradykinin- and PGI_2-, but not NO- induced vasodilation in rabbit hearts.[137] Glibenclamide has no effect on EDHF responses in pig[138] or human[139] coronary arteries. Thus, the general consensus is that K_{ATP} channels play little, if any, role in endothelium-dependent coronary vasodilation (Figure 4aii).

There has been some conflicting evidence regarding the role of K_V channels in endothelium-dependent vasodilation; however, most studies have demonstrated that these channels contribute significantly. Using pig coronary arteries, Cowan and Cohen[140] demonstrated no effect of 4-AP on bradykinin-induced relaxation; however, Thollon *et al.*[141] showed that 4-AP inhibits NO-induced hyperpolarization. The latter is compatible with the effect of NO and iloprost to activate K_V channels in bovine coronary smooth muscle.[67] While Illiano *et al.*[142] have shown that 4-AP has no effect on EDFH-induced relaxation in canine coronary arteries, Nakashima *et al.*[143] have observed an inhibitory effect of 4-AP in the same tissue. Three studies agree that 4-AP inhibits EDHF-induced relaxation in guinea pig coronary arteries.[130,144,145] Our group has demonstrated the role of 4-AP-sensitive K_V channels in regulating basal coronary flow[106,111,146] and our preliminary studies indicate that K_V channels play a large role in endothelium-dependent coronary vasodilation *in vivo* in dogs. These data do not necessarily suggest that K_V channels have a more prominent role in the microcirculation, as 4-AP-induced vasospasm is observed throughout the coronary tree from conduit arteries to resistance arterioles.[147] The overall consensus for K_V channels in endothelium-dependent coronary vasodilation is shown in Figure 4aiii.

Ischemic vasodilation

Large and transient compensatory increases in coronary blood flow follow a brief period of ischemia. This reactive hyperemia represents a repayment of blood flow debt due to the accumulation and washout of ischemic vasodilators. Mediators of ischemic coronary vasodilation have not been identified conclusively. Regardless of what the signaling mechanism might be, it is clear that K^+ channels in CASMC play a large role in reactive hyperemia. Node *et al.* demonstrate that BK_{Ca} channels regulate blood flow to ischemic myocardium in dogs;[121] however, our preliminary studies show that penitrem A, another inhibitor of BK_{Ca} channels, has no effect on reactive hyperemia in pigs.[148] A modest role for BK_{Ca} channels in reactive hyperemia is shown in Figure 4bi. Most studies have focused on the contribution of K_{ATP} channels to ischemic vasodilation. In dogs and pigs, glibenclamide reduces the peak and duration of blood flow repayment following a brief coronary occlusion.[19,20,149–152] No study has addressed whether K_{ATP} channels regulate reactive hyperemia in the human coronary circulation; however, tolbutamide-sensitive channels may regulate this response in the human forearm.[153] The contribution of K_{ATP} channels to reactive hyperemia is summarized in Figure 4bii. We have demonstrated that K_V channels regulate the duration of reactive hyperemia in the canine coronary circulation *in vivo*.[106] 4-AP (300 μmol/L) reduced resting coronary blood flow by approximately 33%. Higher doses of 4-AP reduced coronary flow to the point of causing S-T segment depression, a sign of myocardial ischemia. K_V channels regulate the duration of reactive hyperemia and reduce the repayment of flow debt. Additionally, 4-AP inhibited coronary vasodilation to NO and adenosine, two putative mediators of reactive

hyperemia. The role of K_V channels in coronary reactive hyperemia is shown in Figure 4biii.

Metabolic vasodilation

Myocardial metabolism is the key regulator of coronary blood flow on a beat-to-beat basis, from rest to climbing a flight of stairs or to maximal exercise. Coronary blood flow increases in an almost linear fashion with myocardial oxygen consumption. This very tight coupling between oxygen supply and demand is necessary because the heart has very little capacity for anaerobic metabolism and the myocardium, even at the resting heart rate, consumes approximately 75% of the oxygen delivered to it. Thus, there is very little reserve for oxygen extraction from coronary arterial blood and increases in work done by the heart must be met with parallel increases in coronary blood flow. Unfortunately, at present, we know more about which mechanisms are not responsible for coronary metabolic vasodilation. Further, complexity is added by species-specific differences in responses to exercise and mechanisms underlying them.[79] Thus, much research remains to be done on this central question of coronary physiology. Studies in the last two decades have focused on what K^+ channels may be responsible for this critical physiological phenomenon. BK_{Ca} channels appear to play little, if any, role in coronary metabolic vasodilation.[154] Merkus and colleagues measured coronary blood flow and myocardial oxygen consumption in pigs exercising on a treadmill before and after intravenous treatment with TEA.[154] When one examines the relationship between coronary flow and myocardial oxygen consumption, there is no difference; however, there was a significant reduction in coronary venous oxygen tension.[154] TEA, even at an estimated plasma concentration of 0.6 mmol/L, is not ideal as an inhibitor of BK_{Ca} in exercise hyperemia studies, as TEA is also a ganglionic blocker[155] and reduces heart rate and blood pressure (major determinants of myocardial oxygen consumption) as well as coronary blood flow. We have conducted preliminary experiments with penitrem A, a more selective inhibitor of BK_{Ca} channels, in exercising pigs. Penitrem A has no effect on exercise-induced coronary metabolic vasodilation.[156] The lack of effect of BK_{Ca} channel blockers on the coronary blood flow versus myocardial oxygen consumption is shown in Figure 4ci.

Most studies in this area have focused on the contribution of K_{ATP} channels to coronary metabolic vasodilation. The general consensus is that K_{ATP} channels are not responsible for exercise-induced coronary hyperemia (Figure 4cii). Glibenclamide decreases coronary blood flow at rest in dogs, but has no effect on exercise-induced coronary vasodilation.[19–21,157] In humans, however, glibenclamide attenuates pacing-induced hyperemia.[158] K_{ATP} channels also appear to play a role in pacing-induced hyperemia in dogs.[159] However, comparing pacing and exercise-induced hyperemia is tenuous, as there are fundamental differences in the nature of the vasodilator mechanisms activated (e.g. pacing does not include the sympathetic control mechanisms elicited by exercise[160]). Examples of discrepancies between pacing- and exercise-induced hyperemia have included conclusions made about BK_{Ca} and K_{ATP} channels.[20,156,159,161] If one considers exercise the most physiologically relevant stimulus, then the contribution of K_{ATP} channels to metabolic vasodilation is negligible. In humans performing handgrip exercise, glibenclamide has no effect on exercise-induced forearm blood flow,[162] an observation identical to the lack of effect of glibenclamide on coronary blood flow in exercising animals.

We have investigated the role of K_V channels in coronary metabolic vasodilation.[163] Measuring coronary blood flow and myocardial oxygen consumption in dogs, we demonstrated that intracoronary infusion of 300 μmol/L 4-AP reduced blood flow at rest and attenuated pacing- and catecholamine-induced vasodilation.[163] The inhibitory effect of 4-AP on the relationship between myocardial metabolism and coronary blood flow is significantly more pronounced than has been observed with any other inhibitor of CASMC K^+ channels such as glibenclamide, TEA or penitrem A. These data suggest that K_V channels may be the most important channel type linking myocardial metabolism to coronary blood flow. Unfortunately, however, no study has yet addressed the role of K_V channels in exercise-induced coronary vasodilation. We have suggested that H_2O_2 may be a signaling molecule linking myocardial metabolism to coronary blood flow,[163,164] and others support this idea.[161,165] H_2O_2 activates 4-AP-sensitive K_V channels in CASMC[111] and H_2O_2-induced coronary vasodilation is blocked by 4-AP.[146] The role of K_V channels in coronary metabolic vasodilation is shown in Figure 4ciii.

Dysfunction of CASMC K^+ channels in disease

K^+ channels in CASMC are involved in and affected by many processes related to the pathogeneses of cardiovascular diseases.

Diabetes, hyperglycemia and metabolic syndrome

A number of studies have demonstrated defects in CASMC BK_{Ca} channels in diabetes, hyperglycemia and metabolic syndrome. The activation of BK_{Ca} channels by arachidonic acid in CASMC of Zucker diabetic fatty rats is reduced compared with lean rats; this appears to be secondary to reduced activity of PGI_2 synthase.[166] BK_{Ca} channels in CASMC from Zucker diabetic fatty rats also have a lower Ca^{2+}/voltage-sensitivity due to reduced expression of the regulatory β1 subunit.[167] Diabetes increases BK_{Ca} current in CASMC from conduit arteries of pigs,[168] while spontaneous transient outward currents mediated by BK_{Ca} channels are reduced in arteriolar CASMC from diabetic pigs.[169] We have shown that metabolic syndrome reduces whole-cell penitrem A-sensitive and NS1619-activated BK_{Ca} current in CASMC.[170] K_{ATP} channels in CASMC are also affected by diabetes, as vasodilation due to K_{ATP} channel activation is impaired in human coronary arterioles from patients with type 1 and type 2 diabetes.[94] K_V channel function is negatively impacted by high glucose concentrations *in vitro*. Elevated glucose impairs cAMP-mediated dilation by

reducing K_V channel activity in rat CASMC;[171,172] one mechanism appears to be nitration of the channels.[173] Another mechanism by which diabetes may impair K^+ channel function in CAMSC is through the activation of protein kinase C.[174]

Atherosclerosis and ischemia

Hypercholesterolemia impairs coronary vasodilation mediated by K^+ channels.[175] In pigs, high blood cholesterol has been reported to increase[168] and decrease[176] BK_{Ca} current in CASMC. The contribution of K_V channels to adenosine-mediated dilation of pig coronary arterioles is abolished by hypercholesterolemia.[108,176,177] Further, K_V currents in porcine CASMC are reduced by high blood cholesterol.[108,176–178] Homocysteine, an independent risk factor for atherosclerosis, inhibits BK_{Ca} channels in pig CASMC.[179] BK_{Ca} channels in smooth muscle cells from coronary plaque have a higher activity than those in normal CASMC.[180] Further, compared with normal CASMC, the BK_{Ca} channels of CASMC from atherosclerotic plaques respond differently to growth factors.[181] BK_{Ca} channels contribute significantly to endothelium-dependent vasodilation in the ischemic myocardium of dogs.[121,182] K_{ATP} and K_V channels compensate to preserve hypercapnic coronary flow when NO production is absent.[183] Acute hypoxia dilates guinea pig hearts[184] and pig coronary arteries and arterioles[185,186] through the activation of K_{ATP} channels; however, in rabbit coronary arteries, K_{ATP} channels are not involved.[187] Chronic hypoxia has opposite effects on K_V current magnitude in right and left CASMC from rats, suggesting differences in K_V channel isoforms or signaling mechanisms.[188] Acidosis increases K_V, but not BK_{Ca} or K_{ATP}, current in rat CASMC;[189] however, acidosis dilates pig coronary arterioles through a glibenclamide-sensitive mechanism.[190,191] Lactate, a metabolite produced during myocardial ischemia, activates BK_{Ca} channels in pig CASMC.[192]

Hypertension, cardiac hypertrophy and cardiomyopathy

Aldosterone, a mineralocorticoid with relevance to hypertension, reduces BK_{Ca} channel expression and iberiotoxin-sensitive relaxations in murine coronary arteries.[193] BK_{Ca} channels compensate for a loss of endothelial function in coronary arteries of rats made hypertensive with ouabain.[194] Genetic ablation of K_{ATP} channels causes hypertension and coronary vasospasm in mice.[96,98] BK_{Ca} current is reduced in CASMC from rats and rabbits with left ventricular hypertrophy, attributable to a reduction in single channel amplitude and Ca^{2+}/voltage sensitivity.[195] K_{ATP} channels are normally not involved in coronary metabolic vasodilation; however, K_{ATP} channels become important for exercise-induced hyperemia in dogs with left ventricular hypertrophy.[196] K_V current is increased in CASMC from rats with right ventricular hypertrophy due to pulmonary hypertension.[188] BK_{Ca} channels compensate for the loss of NO-dependent coronary artery relaxation in cardiomyopathic hamsters.[197] The role of K_{ATP} channels in coronary vascular regulation changes in the remodeled left ventricle of swine with a 2–3-week-old myocardial infarction.[198] Specifically, in normal pigs, K_{ATP} channels are not required for exercise-induced coronary vasodilation; however, following an infarction, K_{ATP} channels are responsible for a significant portion of exercise hyperemia.

Aging and reactive oxygen species

Aging is the main risk factor for coronary heart disease and spontaneous contractile activity is higher in coronary arteries of the aged, consistent with the idea that reduced K^+ channel expression or activity is related to coronary vasospasm.[17] Aging reduces BK_{Ca} channel current and pore-forming α subunit protein in CASMC from rats and humans.[199] Similarly, the expression of the regulatory $\beta 1$ subunit of BK_{Ca} channels is reduced in CASMC from aged rats.[200] Menopause, part of the aging process in women, reduces estrogen levels; this may also influence BK_{Ca} channel activity and coronary artery reactivity. Estrogen increases BK_{Ca} channel activity in human CASMC and iberiotoxin inhibits estrogen-induced coronary artery relaxation.[201,202] Reactive oxygen species are signaling molecules involved in normal coronary physiology as well as pathophysiology. H_2O_2 relaxes pig coronary arteries and arterioles via BK_{Ca} channels[85,203] and dilates the canine coronary circulation through the activation of K_V channels.[111,146] Peroxynitrite, the product of a reaction between NO and superoxide anion, inhibits BK_{Ca} channels in human CASMC; superoxide alone was without effect.[204] Peroxynitrite also inhibits K_V current in rat CASMC,[173] as does superoxide, which inhibits cAMP-mediated dilation by reducing K_V channel function in the coronary arteries of diabetic rats.[205]

Summary of K^+ channels in coronary blood flow

BK_{Ca}, K_{ATP} and K_V channels are important in various aspects of coronary vascular regulation. K_{ATP} and K_V channels are important in determining basal coronary microvascular tone, whereas BK_{Ca} channels do not appear to contribute to resting coronary flow. BK_{Ca} and K_V channels participate in endothelium-dependent coronary vasodilation, while K_{ATP} channels appear to play no role. All three channels seem to contribute in some way to ischemic coronary vasodilation. Only K_V channels are mediators of coronary metabolic vasodilation, as inhibitors of K_{ATP} and BK_{Ca} channels have no effect on coronary blood flow elicited by metabolic demands. Diabetic conditions impair the function of BK_{Ca}, K_{ATP} and K_V channels in CASMC. The expression and activity of CASMC BK_{Ca}, K_{ATP} and K_V are altered by hypercholesterolemia, ischemia, hypoxia, hypertension, myocardial hypertrophy and cardiomyopathy. Aging decreases the function and expression of BK_{Ca} channels, while reactive oxygen species have physiological and pathophysiological effects on the activity of BK_{Ca} and K_V channels. Overall, K_V channels may have the most central role in regulating coronary blood flow, as these channels

are involved in resting vascular tone, as well as endothelium-dependent, ischemic and metabolic vasodilation.

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