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Coronary microvascular Kv1 channels as regulatory sensors of intracellular pyridine nucleotide redox potential

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Abstract

Smooth muscle voltage-gated potassium (Kv) channels are important regulators of microvascular tone and tissue perfusion. Recent studies indicate that Kv1 channels represent a key component of the physiological coupling between coronary blood flow and myocardial oxygen demand. While the mechanisms by which metabolic changes in the heart are transduced to alter coronary Kv1 channel gating and promote vasodilation are unclear, a growing body of evidence underscores a pivotal role of Kv1 channels in sensing the cellular redox status. Here, we discuss current knowledge of mechanisms of Kv channel redox regulation with respect to pyridine nucleotide modulation of Kv1 function via ancillary Kvβ proteins as well as direct modulation of channel activity via reactive oxygen and nitrogen species. We identify areas of additional research to address the integration of regulatory processes under altered physiological and pathophysiological conditions that may reveal insights into novel treatment strategies for conditions in which the matching of coronary blood supply and myocardial oxygen demand is compromised.

Keywords

ion channels; vascular smooth muscle; endothelium; vasodilation; NADH

1. Introduction

Excitable cells utilize ionic gradients across biological membranes to enable numerous life processes. In this respect, the intracellular environment is rich in potassium ions, and transmembrane voltage-dependent potassium (Kv) channels are widely expressed to control the electrical properties of both eukaryotic and prokaryotic cells. Kv channels, due to their broad phyletic distribution and genetic diversity, are thought to be the oldest of voltage-gated

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ion channels. Mammalian excitable cells express a number of Kv channel subtypes that work in concert to regulate membrane potential [40]. Through their ability to sense changes in membrane voltage, these channels rapidly respond to depolarization by altering the conformation of their gating apparatus to allow potassium efflux, reducing intracellular positive charge and thus changing the membrane potential to a more hyperpolarized state. In this manner, the activity of Kv channels contributes to the regulation of neuronal action potential firing, muscle contraction, and hormonal secretion. In excitable cells of the cardiovascular system, the coordinated K^+ efflux by numerous Kv channel subtypes promotes physiological processes such as cardiac action potential repolarization and vascular smooth muscle (VSM) relaxation.

Smooth muscle cells of the vasculature have been reported to express channel subtypes belonging to the Kv1, Kv2, Kv3, Kv4, Kv6, Kv7, Kv9 and Kv11 families (see reference [25], in this issue). In addition to their regulation by membrane voltage, Kv channels are sensitive to functional modulation by a wide variety of intracellular signaling pathways. In small arteries and arterioles of the microcirculation, these pathways tune local and regional blood flow in response to endogenous vasoconstrictor and vasodilator stimuli. In the coronary microcirculation, recent evidence has revealed the importance of redox-mediated Kv1 functional upregulation for physiological enhancement of blood flow (i.e., ‘functional’ or “metabolic” hyperemia), that occurs during periods of increased cardiac oxygen consumption (e.g., during increased heart rate and ventricular contractility) [19,46,47]. While the underlying cellular and molecular mechanisms connecting the level of oxygen demand of cardiomyocytes in an active heart to the redox regulation of Kv1 function in coronary arterial myocytes are not clear, this process likely involves the complex coordination of multiple contributing pathways. Indeed, a thorough understanding of these mechanisms could aid the rational development of novel strategies to improve the coupling between oxygen supply and demand in the heart, which is impaired in a number of conditions such as hypertension, diabetes mellitus, heart failure, and coronary artery disease [6,12,13,17,64,72].

Here, we discuss the known role for Kv1 in linking cellular metabolism to regulation of coronary blood flow. A brief discussion of redox-dependent mechanisms of Kv1 channel regulation with respect to the control of coronary blood flow is followed by a review of Kv1 structural features and the potential role for modulation of channel activity via sensing of changes in cellular pyridine nucleotide status by the regulatory auxiliary Kvβ subunits. This is followed by a condensed review of direct influence of reactive oxygen species and reactive nitrogen species on Kv1 channel function. We emphasize cellular redox changes following altered myocardial workload and how these may be sensed by Kv1 channels in the coronary vasculature to promote VSM hyperpolarization and vasodilation to match blood flow with metabolic demand in the heart.

2. Physiological role of Kv1 channels in coronary functional hyperemia

Unlike other organs, the heart extracts most of the oxygen delivered to it by the arterial blood supply at rest [3]. With little reserve for further oxygen extraction, enhancement of pump activity (e.g., during exercise) and greater demand for oxygen by the myocardium

must be coupled with dilation of the coronary arteries and arterioles to instantaneously increase blood flow. This hyperemic response is crucial for maintenance of proper pump function via prevention of myocardial ischemia during periods of increased workloads. While extensive research efforts have aimed to reveal the signaling pathways responsible for metabolic hyperemia in the heart, the mechanisms underlying this process remain poorly understood. In the search for a molecular link between vascular function and myocardial metabolism, decades of pharmacological studies employing receptor and ion channel blockade have yielded controversial conclusions [3,4,15,36,37,55,63,73,74]. The vasoactive metabolite adenosine, which is released from active cardiomyocytes, was long postulated as a primary mediator of coronary artery dilation in response to increase cardiac workload [3]. Yet, studies have shown that administration of adenosine receptor blockers fails to disrupt the normal relationship between myocardial oxygen consumption, coronary vasodilation and blood flow during exercise [4,15,74]. Intriguing results of a study by Tune et al. demonstrated that simultaneous blockade of adenosine receptors, K_{ATP} channels, and nitric oxide synthesis, failed to lower coronary blood flow in exercising dogs [73], suggesting a critical role for an alternative mediator of hyperemia.

A growing body of evidence now supports the concept that coronary hyperemia requires activation of smooth muscle Kv1 channels via a redox-dependent mechanism. For example, a study by Dick et al. reported that the Kv channel blocker 4-aminopyridine decreases coronary blood flow at rest and reduces normalized debt repayment ratio during reactive hyperemia [14]. Moreover, mice in which Kv1.5 is genetically ablated have significantly blunted hyperemic responses to increases in cardiac work via administration of norepinephrine, yet the normal relationship between cardiac work and myocardial blood flow is restored when Kv1.5 is selectively reconstituted in smooth muscle on an otherwise Kv1.5-null background [46], strongly suggesting that loss of hyperemia in the Kv1.5-null animals occurs due to the absence of these channels from the coronary arterial myocytes. These results were corroborated in a separate investigation in which in vivo administration of correolide, a selective Kv1 channel blocker, decreased blood flow in response to dobutamine challenge and inhibited blood flow repayment during reactive hyperemia [19]. Interestingly, mice lacking Kv1.3 subunits also exhibit decreased myocardial blood flow in response to increases in cardiac work, [47], suggesting a potential role of heteromeric Kv1 channels in mediating metabolism-dependent vasodilation. In vitro work has also indicated that vasodilation of coronary arteries to H_2O_2, a purported metabolic vasodilator of coronary arteries, is sensitive to the thiol reductant dithioerithritol and 4-aminopyridine, but not the BK_{Ca} channel inhibitor iberiotoxin [56,57]. These results suggest that Kv channels in VSM may respond to redox-modulating myocardial derived metabolites to induce coronary vasodilation.

While Kv1 channel activity has been implicated as an important regulator of human vascular tone, suppression of Kv1 function may contribute to vascular pathologies. Consistent with this, a recent study found that inhibition of H_2O_2-induced dilation by DPO-1, a selective Kv1.5 channel blocker, was attenuated in arterioles from patients with coronary artery disease, suggesting a reduced capacity for Kv1-dependent vasodilator function [43]. Thus, an improved understanding of mechanisms linking cellular metabolism and vascular Kv1 channel function is essential, as this process likely becomes compromised during pathology.

In the following sections, we discuss redox regulation of Kv1 channels with respect to intracellular pyridine nucleotides and reactive oxygen and nitrogen species and how channel function may be altered to influence coronary vascular tone and myocardial blood flow via these mediators.

3. Mechanisms of Kv1 regulation by cellular pyridine nucleotide redox

Structurally, channels of the Kv1 family share a similar pore complex consisting of four individual α subunits. Each subunit consists of six transmembrane segments (S1–S6) with S1–S4 forming the voltage sensor complex while S5 and S6 form the pore region, together with the S4–S5 linker comprising the gating apparatus [33]. Voltage-sensitivity is conferred by a group of highly conserved positive residues within each S4 segment [1], which render the channel responsive to depolarization. Members of one Kv subfamily can co-assemble with each other to form heterotetrameric pore complexes, an attribute thought to contribute to greater functional diversity of Kv membrane potential regulation [9]. Pore-forming Kv subunits are known to assemble with a variety of intracellular ancillary subunits such as the Kvβs [52]. Like the α pore subunits, the Kvβ proteins can also assemble as heterotetramers [54,61], and extend the structure of the channel by approximately 30 Å into the cytosolic compartment [33]. Each β protein binds an α subunit at a T1 docking domain (Fig. 1), which interacts with the voltage sensor and may constrain its conformation [11,34], thus providing a plausible means of regulating the voltage sensitivity of the channel.

A primary mode of regulation of Kv1 in the coronary arteries and arterioles could conceivably arise via specific α/β interactions. The Kvβ proteins were found in an early study to share significant identity with proteins belonging to the aldo-keto reductase (AKR) superfamily [39]. The AKR enzymes catalyze the reduction of carbonyl substrates to primary and secondary alcohols in a manner requiring hydride transfer from a nicotinamide adenine dinucleotide (i.e., NAD(P)H) cofactor. Structurally, the Kvβs share key features with other AKR proteins, including an α_8/β_8 barrel and key amino acid residues that are required for catalysis and NAD(P)(H) binding. Consistent with other AKRs, the model three-dimensional structure of the Kvβ2 homotetramer revealed high affinity binding of $NADP^+$ within a deep cleft of the active site [21,22]. The reasons for the pairing between a reductase and a voltage-gated potassium channel persisting in a number of excitable cell types are not known. However, interactions between the active site of Kvβ with the α subunit voltage sensor support the notion that there may be functional coupling between Kv channels and β-subuits such that either (1) the catalytic activity of Kvβ could be controlled by voltage-dependent channel gating via conformational changes in the active site, or perhaps more likely (2) that Kv activity could be differentially affected by catalysis or cofactor oxidation at the active site of Kvβ via conformational changes in the voltage sensor affecting the Kvβ protein.

Numerous reports support the concept that Kvβ proteins strongly influence Kv1 channel function (see reviews [52] and [27]). Studies in heterologous expression systems demonstrate that co-expression of Kvβ with Kvα subunits confers rapid inactivation to otherwise non-inactivating K^+ currents and shifts the voltage-dependence of channel activation towards more negative membrane potentials [52]. Several lines of evidence now

suggest the potential importance of Kvβ as a functional sensor of cellular metabolic status such that biochemical modification upon binding pyridine nucleotide cofactors modifies channel gating [27,50,77]. Purified Kvβ proteins have been demonstrated to exhibit catalytic function with a wide range of aldehyde and ketone substrates, albeit their in vitro catalytic efficiency is remarkably low relative to other known AKRs [28,69]. Nonetheless, all Kvβ proteins bind to both oxidized (i.e. $NAD(P)^+$) and reduced (NAD(P)H) pyridine nucleotide cofactors with affinities in the low micromolar range, which is well below normal intracellular levels [5,18]. Moreover, the activation and inactivation properties of Kv1α/β channels are sensitive to the redox state of NAD(P)(H) that interacts with the Kvβ subunits. For example, Tipparaju et al. demonstrated that although non-inactivating currents mediated by Kv1.5 expressed alone in COS-7 cells are insensitive to pyridine nucleotides applied via the patch pipette solution, application of NAD(P)H increased total inactivation and shifted the voltage-dependence of inactivation and activation towards more negative membrane potentials relative to when $NAD(P)^+$ was applied in cells co-expressing both Kv1.5 and Kvβ1.3 [71]. A reduction in Kvβ1-medated channel inactivation upon application of $NADP^+$ was also observed for Kv1.1 channels [49]. Similar results were shown for Kv1.5 channels co-expressed with Kvβ3 subunits [70], which similar to Kvβ1, also contain an N-terminal inactivation domain [52]. Redox modulation of channel inactivation by pyridine nucleotides appears to require both the C-terminal region of the Kv1α protein and electrostatic interactions between the N-terminal region and AKR enzymatic core of the β protein [50,70]. In contrast to effects of pyridine nucleotides on cells expressing Kv1/Kvβ1 and Kv1/Kvβ3 couples, channel inactivation is unchanged by coexpression of Kv1/Kvβ2, which likely reflects the lack of an N-terminal inactivation domain on the Kvβ2 subunit (Fig. 1) [52]. Nonetheless, a robust negative shift in the voltage-dependence of activation of Kv1 channels interacting with Kvβ2 is observed in the presence of reduced pyridine nucleotides [70]. Despite the availability of data demonstrating differential regulation of Kv1 activity by oxidized versus reduced redox couples, the in vivo relevance of these phenomena has not been demonstrated.

The functional role for Kvβ proteins in modulating vascular Kv1 channel activity in vivo and tone regulation are currently lacking, yet several studies have reported the expression profiles of Kv1/Kvβ proteins in various vascular beds. Acute inhibition of Kv1 channel activity is considered a primary contributor to hypoxic pulmonary vasoconstriction (HPV) [2] and Kvβ subunits have been proposed as determinants of redox sensing capacity of Kv1 channels for oxygen tension in the lung parenchyma [10]. Primary cultures of rat arterial myocytes derived from branches and left and right main pulmonary arteries express transcripts for several Kv1α members as well as Kvβ1.1, Kvβ2, and Kvβ3 subunits [83], yet the specific contribution of these subunits to the HPV response remains unclear. In small mesenteric arterial smooth muscle of rats, mRNA encoding Kvβ1, Kvβ2 and Kvβ3 is present [79]. Whereas, in rabbit portal vein, mRNAs for Kvβ1.1, β1.2, and β2, but not β3.1, are detectable [68]. A recent study examining Kv1 expression in human adipose arterioles revealed mRNA expression of three splice variants of Kvβ1 (i.e., β1.1, β1.2 and β1.3) in these vessels [43]. Note that while many early studies investigating the molecular identity of delayed rectifier 4-aminopyridine-sensitive K^+ currents in VSM have mostly examined gross mRNA and protein levels in crude ex vivo artery preparations, further characterization of

regional variations in subunit stoichiometry of heteromeric channel structures in the vasculature at the molecular level have remained largely unexplored. Considering the marked differences in channel regulation imparted by the diverse repertoire of channel subunits, distinct bed-specific expression patterns of Kvα and β subunits may indeed reflect differences in the demand for redox regulation for control of organ perfusion and should be revisited with newly available advanced technologies and experimental approaches. Furthermore, altered channel composition following more sustained changes in metabolic demand could represent an important microvascular adaptation in vivo that may become compromised to varying degrees in disease states, and adversely affect vascular resistance and tissue oxygenation.

To begin to examine the aforementioned issues, we recently examined the molecular identity of Kvβ proteins that are expressed in the murine coronary circulation [45]. In first and second order left anterior descending coronary arteries, we found mRNA transcripts for Kvβ1, Kvβ2 and Kvβ3. At the protein level, Kvβ1 and Kvβ2 were detected by Western blot, whereas in situ proximity ligation analyses suggested that both of these Kvβ isoforms interact with Kv1.5 subunits in native coronary Kv channels [45]. Additionally, our results suggest that Kvβ1 and Kvβ2 may assemble as heterotetramers in a subpopulation of Kv1 channels in coronary arterial myocytes. These findings may have important implications for arterial function in regards to redox regulation of smooth muscle contractility and blood flow. For example, as mentioned above, Kvβ2 is structurally and functionally unique among the Kvβ proteins in that it lacks the N-terminal inactivating domain found in Kvβ1 and Kvβ3, which occludes the channel pore to confer rapid inactivation to otherwise non-inactivating Kv currents. Thus, the functional influences of these ancillary subunits on Kv1 activity in response to changes in NAD(P)H:NAD(P)$^+$ could oppose each other. Experiments performed in COS cells suggest that Kvβ2 subunits can indeed mask the inactivation function of Kvβ1 [80], yet the net effect of Kvβ complexes consisting of more than one Kvβ isoform on the gating properties of native vascular Kv1 channels remains unknown. Nonetheless, given that smooth muscle contractility is strongly influenced by relatively small changes in membrane potential [41,42], Kvβ may couple vascular function to cellular metabolism by modulating the Kv1 window current (Fig. 2). Considering that a subpopulation of Kvβ subunits induces time-dependent inactivation of Kv1 channels, only a fraction of channels in association with these subunits may be available at steady state membrane potentials in coronary arterial myocytes. With the remainder of channels lacking the dominant inactivation function, the Kvβ-induced negative shift in voltage-dependence of activation may represent a key contributor to greater macroscopic current upon changes in cellular metabolic status. While the functional relevance of this balance is currently unclear, divergent functional regulation of Kv1 by distinct auxiliary subunits in association with the channel pore complex may also contribute to fine tuning of Kv1 function with respect to coupling of local blood flow with metabolic demands of the local tissue environment.

Importantly, a number of factors could participate in transient or sustained modulation of intracellular pyridine nucleotide redox ratio in VSM upon increases in heart rate and ventricular contractility. These include systemic circulating factors (e.g., bFGF, IL-1β, TNFα, lactate) as well as diffusible factors released into the interstitium by the active myocardium (e.g, H_2O_2, adenosine) and a set of myocyte or endothelial-derived growth

factors.[29,35,48,62,76] Additionally, while the heart does not itself undergo sustained hypoxia under physiological conditions, myocardial oxygen consumption is markedly increased during moderate to intense exercise and augmented demand for oxygen by cardiomyocytes could siphon oxygen from the vascular wall, thereby producing a local modest oxygen-deprived microenvironment to promote accumulation of reduced pyridine nucleotides in VSM [78]. However, it remains possible that discrepancies may exist in the regulation of pyridine nucleotide redox between vascular beds. Thus, a detailed assessment of the relationship between vascular smooth muscle pyridine nucleotide redox and cardiac oxygen demand would be valuable to future studies addressing the role of Kvβ:NAD(P)(H) interactions in the control of blood flow to the heart. Moreover, future studies employing knock-in strategies to target key residues in the Kvβ subunits (e.g., Tyr^{90} of Kvβ2) [38,69] are needed to evaluate the specific in vivo roles for oxido-reductase catalytic function versus cofactor binding, in Kv1-mediated vasodilation.

4. Direct influence of reactive oxygen and nitrogen species on vascular Kv1 function

Elevated levels of reactive oxygen species (ROS) likely contribute to the control of coronary Kv channel function. Experiments examining human, rodent and large animal coronary arterioles have demonstrated that hydrogen peroxide (i.e., H_2O_2), a product of superoxide dismutation, functions as a cardiomyocyte- and endothelium-derived physiological vasoactive agent that can freely diffuse across the plasma membrane and hyperpolarize VSM membrane potential via direct and indirect modulation of K^+ channel activity [31,56,57,60,84]. Direct functional regulation of Kv channels by oxidative agents may occur via modification of specific cysteine, methionine, histidine and tyrosine residues within the channel complex [59]. In particular, early studies using expression of cloned mammalian Kv subunits in Xenopus oocytes have suggested that oxidation of N-terminal cysteine residues within both the Kvα and β subunits inhibits channel inactivation, possibly due to rapid and reversible disulphide bridge formation between the inactivation gate and a neighboring site within the channel complex [54,58] Application of H_2O_2 was also shown to augment peak Kv current, shift the voltage-dependence of channel activation toward more negative membrane potentials, and accelerate channel activation in CHO cells expressing Kv1.5, in the absence of Kvβ co-expression [7]. A recent study in mesenteric arterial myocytes suggests that H_2O_2-mediated Kv potentiation may also occur via incorporation of glutathione in the channel protein at cysteine residues [51], which has also been suggested to promote activation of Cav1.2 voltage-dependent calcium channels [67]. However, in the presence of heightened oxidative stress, H_2O_2 fails to further activate Kv channels and may even lead to channel inhibition, thus supporting a bidirectional functional influence of oxidative modification, depending on the redox state of the cell.

Superoxide production by the mitochondria can also lead to the formation of peroxynitrite ($ONOO^-$) via reaction with nitric oxide [26]. $ONOO^-$ is known to be highly reactive with tyrosine residues and can alter the function of cellular proteins, including voltage-gated ion channels [32]. In addition to numerous pathways by which nitric oxide and reactive nitrogen species could influence Kv-mediated vasodilation [16,44,66,81], channel activity could be

directly altered by reaction of $ONOO^-$ with channel proteins. In coronary arteries of rats, increased production of $ONOO^-$ may impair Kv-mediated vasodilation via nitration of tyrosine residues in Kv1.2 subunits [30]. In addition to nitration of tyrosine residues, S-nitrosothiols, like S-nitroso-N-actylpenicillamine (SNAP), have been shown to modify cysteines in the L-type Ca^{2+} channel through multiple mechanisms including transnitrosation, mixed disulfide bonds, and disulfide bond formation between cysteines [24]. A biotin-switch assay revealed the presence of S-nitrosylated cysteine residues in SNAP-treated ltk^- cells stably expressing human Kv1.5. Through molecular modeling, two cysteines in the S2 segment (i.e., C331 and C346) were identified as a potential site of S-nitrosylation, as S-nitrosothiol groups at these cysteines could be stabilized by hydrogen bridge bonds with I262, located in S1, and R342, located in S2. Interestingly, this modification correlated with a reduction in Kv1.5 current density. Although direct modification identified thus far at cysteine and tyrosine residues generally appears to be associated with channel inhibition, it is unclear whether direct modification of Kv channels by NO-derived factors impacts the regulation of coronary vasomotor tone and myocardial blood flow. Nonetheless, nitration of Kv channels may impair vasodilatory function in the presence of pathological conditions in which superoxide production is elevated, such as hyperglycemia and diabetes. Future work is needed to address the precise functional consequences of specific tyrosine and cysteine modifications within the Kv channel complex and the differential effects conferred by α/β subunit compositions in the context of physiological and pathological regulation of coronary vasodilation.

6. Summary

Kv1 channels in the microcirculation are capable of sensing cellular redox state by a variety of mechanisms which ultimately act in concert to control VSM membrane potential to adapt blood flow to constantly changing metabolic conditions (Fig 3). In addition to their regulation by pyridine nucleotide redox and reactive oxygen/nitrogen species discussed here, Kv1 channel subunits can be functionally modulated by a number of other modifications including phosphorylation, palmitoylation, and glycosylation [20,23,75]. Future work using in silico modeling could help shape a better understanding of how this complex network of pathways works in an integrated fashion to influence vascular function in a variety of physiological and pathological states. Advanced gene editing technology now offers an exceptional tool to determine precise sites of redox sensing within the channel structure in the setting of native channels of the vasculature. Importantly, a number of both gain-of function and loss-of-function mutations have been identified in Kv1 channel subunits [8,53,65,82]. In addition to the impact that these mutations likely have on cardiac and neuronal repolarization, it is plausible that altered coupling between myocardial metabolism and coronary blood flow may also contribute to cardiovascular disease in patients harboring these mutations. Thus, future advances in our understanding of redox regulation of coronary Kv channels during disease states could ultimately lead to improved strategies to enhance coupling between metabolic demand and myocardial blood flow for therapeutic benefit.

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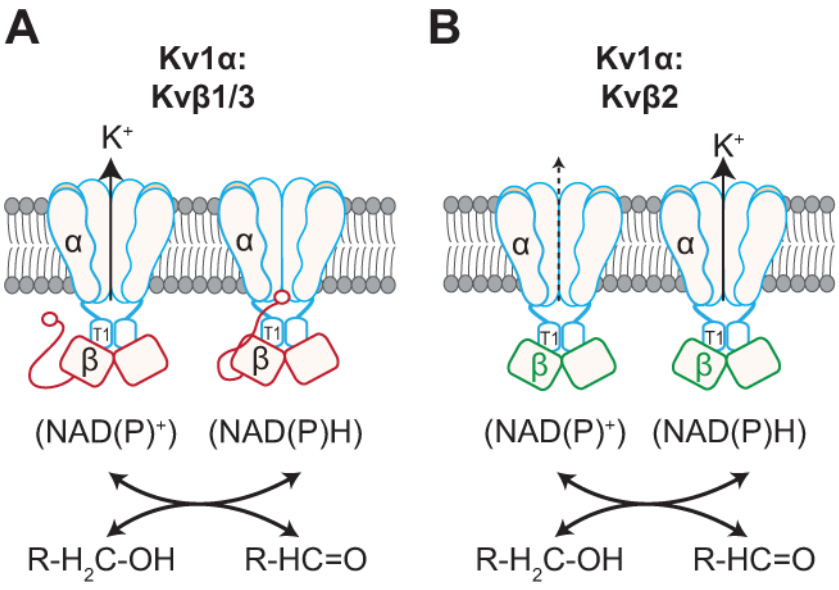

Figure 1. Kvβ-dependent regulation of Kv1 activity by pyridine nucleotide cofactors

(**A**) Regulation of Kv1 function by Kvβ1 and Kvβ3 subunits, which possess NH_2-terminal ball-and-chain-like inactivation. Inactivation is enhanced by bound pyridine nucleotides in their reduced form (i.e., NAD(P)H). (**B**) Regulation of Kv1 function by Kvβ2 subunits. Kvβ2 proteins lack the NH_2-terminal inactivation domain. Voltage-dependence of activation is shifted towards more negative membrane potentials in the presence of reduced pyridine nucleotide cofactors. Transition between states can occur by exchange of pyridine nucleotides or by catalytic activity to oxidize bound pyridine nucleotide cofactors.

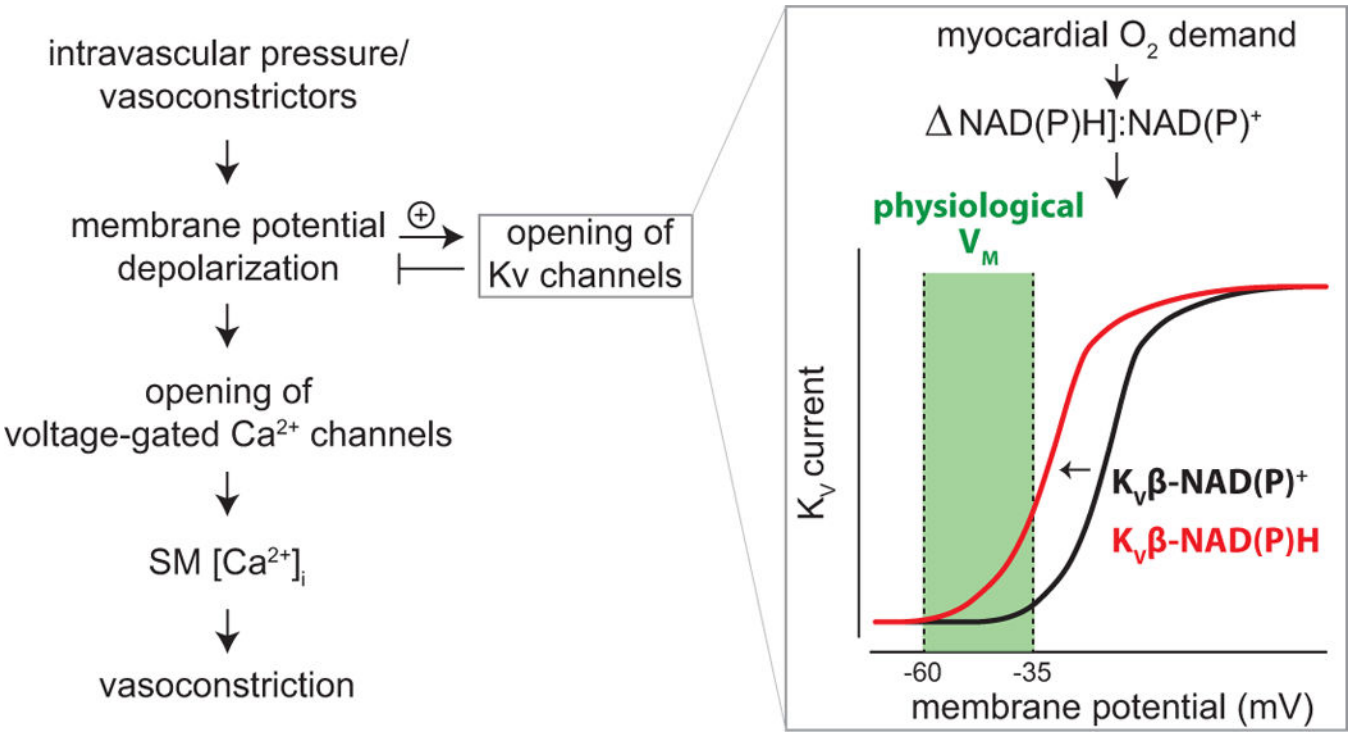

Figure 2. Hypothetical model of coronary blood flow regulation by pyridine nucleotide-mediated activation of Kv1 channels

Flow diagram on the left shows role of smooth muscle Kv channels in opposing membrane potential depolarization and vasoconstriction. Expanded window shows proposed model of Kv1 activation during periods of elevated cardiac workload. In this scheme, increases in myocardial oxygen demand leads to changes in pyridine nucleotide redox status in coronary arterial myocytes. Accumulation of reduced pyridine nucleotides could shift the threshold and voltage-dependence of activation of available Kv1 channels further into the narrow window of physiological steady-state membrane potential in arterial myocytes of pressurized arteries and arterioles (−60 to −35 mV), thereby significantly increasing Kv1 activity leading to membrane hyperpolarization, vasodilation, and enhanced blood flow.

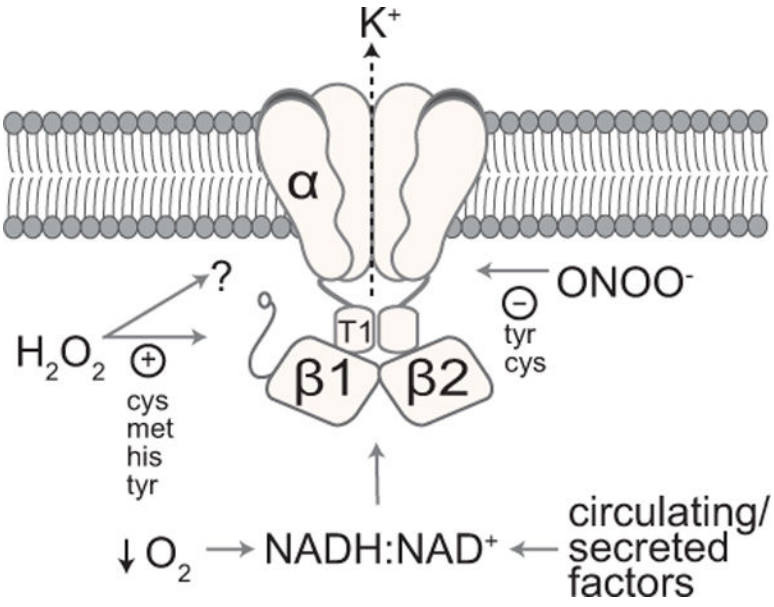

Figure 3. Coronary smooth muscle Kv1 channel modulation by cellular redox

Shown are the major discussed pathways which could contribute to functional alteration of Kv1 activity upon changes in myocardial oxygen demand.