Silent Inward Rectifier K⁺ Channels in Hypercholesterolemia

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Hypercholesterolemia is an independent risk factor for development of cardiovascular disease and has been demonstrated to impair endothelium-dependent and independent vasodilatation. However, the mechanisms responsible for changes in vascular reactivity and impaired blood flow regulation induced by hypercholesterolemia remain unclear. Previous studies in cultured endothelial cells have shown that cholesterol impairs whole-cell Kᵢᵣ channel currents. Levitan and colleagues in this issue of Circulation Research extend these findings to show that exposure of endothelial cells to pathophysiologically relevant concentrations of acetylated low density lipoprotein (LDL) or very low density lipoprotein (vLDL) leads to membrane cholesterol enrichment, and also inhibits endothelial Kᵢᵣ channel currents and shear stress–induced activation of these channels. More importantly, the authors show, for the first time, that in freshly isolated endothelial cells from hypercholesterolemic pigs, Kᵢᵣ channel currents are impaired, and that this inhibition can be reversed by methyl-β-cyclodextrin. Thus, hypercholesterolemia can be added to the list of pathophysiological states that appear to inhibit the function of vascular Kᵢᵣ channels, including hypertension and diabetes. What remains unclear is the mechanism by which elevated membrane cholesterol silences endothelial Kᵢᵣ channels, the generality of these findings to Kᵢᵣ channels expressed in vascular smooth muscle cells, and the significance of cholesterol modulation of endothelial or smooth muscle Kᵢᵣ channels in resistance arteries and arterioles, vessels that participate in the regulation of blood pressure and blood flow.

A number of ion channels, in addition to Kᵢᵣ channels, appear to associate with cholesterol-rich lipid rafts, and changes in membrane cholesterol content have been shown to modulate the function of several ion channels. However, the mechanisms responsible for targeting channels to lipid rafts and how cholesterol modulates channel function have not been established. Endothelial cells appear to express predominantly Kir 2.1 and 2.2 Kᵢᵣ channels. When expressed in Chinese hamster ovary (CHO) cells, these channels show similar sensitivity to membrane cholesterol as native endothelial Kᵢᵣ channels. Furthermore, in this expression system, cholesterol-induced changes in whole-cell Kᵢᵣ channel currents are not affected by inhibition of protein synthesis, and are not associated with changes in cell surface expression of Kir 2.X channels, nor in the single channel currents through these channels. These data suggest that cholesterol-induced changes in Kᵢᵣ channel currents do not involve alterations in channel expression, trafficking, or modulation of single channel conductance, activation or inactivation kinetics. Instead, cholesterol seems to cause Kir 2.X channel to become “silent”. Interestingly, Kir2.3 channel proteins are less sensitive to cholesterol than other Kir2.X family members, which may provide a molecular clue to the identity of the portion of these channels involved in modulation by cholesterol.

Vascular smooth muscle cells also express Kir2.1 channels that importantly determine the reactivity of vessels to changes in extracellular K⁺, and may be involved in functional regulation of blood flow in tissues such as the heart and the brain. Cholesterol appears to exert similar effects on native Kir 2.X channels expressed in endothelial cells and channels expressed in CHO cells. Thus, it seems likely that hypercholesterolemia also may impact smooth muscle Kᵢᵣ channels and potentially profoundly affect the regulation of vascular smooth muscle tone independent from, or in addition to, effects on endothelial Kᵢᵣ channels.

Although there is considerable experimental evidence supporting a physiological role for Kᵢᵣ channels in vascular smooth muscle cells in the wall of resistance arteries and arterioles, particularly in the brain and heart, the functional role of endothelial Kᵢᵣ channels in vessels that impact regulation of blood pressure and blood flow has not been well studied. First, it seems unlikely that endothelial cell Kᵢᵣ channels significantly participate in the regulation of resting endothelial cell membrane potential in resistance arteries and arterioles, because endothelial cell membrane potential in these vessels is approximately −30 mV, and studies of Kᵢᵣ channel currents in freshly isolated arteriolar endothelial cells (Figure 1) suggest that Kᵢᵣ channels contribute little if any current at this potential. However, because of the shape of the current–voltage (I–V) relationship for these channels (Figure 1), and the relatively depolarized membrane potentials in resistance vessels, outward currents through Kᵢᵣ channels may be activated simply by membrane hyperpolarization (Figure 2). Thus, Kᵢᵣ channels may act to amplify hyperpolarization induced by other K⁺ channels and may contribute to endothelium-dependent vasodilation (Figure 2). This mechanism could provide an explanation for Ba²⁺ sensitivity of bradykinin-induced dilation reported in human forearm. Hyperpolarization-induced activation of currents through endothelial Kᵢᵣ channels also may provide a mecha-

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Hypercholesterolemia and KIR Channels

Inward rectifier K+ (KIR) channel currents in freshly isolated arteriolar endothelial cells. Data are means ± SE (n = 5) Ba2+-sensitive (100 μmol/L) difference currents measured using the perforated patch technique in the presence of 5 mmol/L or 15 mmol/L K+ in the extracellular fluid in freshly isolated endothelial cell tubes. At the resting membrane potential of these cells (∼30 mV), in normal extracellular K+ (5 mmol/L), there is little or no outward current. However, membrane hyperpolarization induced by opening of other endothelial K+ channels could recruit outward current through KIR channels, amplifying the original hyperpolarization. Also note that with an increase in extracellular K+, the current–voltage relationship shifts to more depolarized potentials such that outward current through the KIR channels is present. This would tend to hyperpolarize the cells toward, in this case, −45 mV. Figure reproduced with permission from Jackson.14

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Figure 2. Potential role of endothelial KIR channels in the regulation of vascular tone. Endothelium-dependent vasodilator agonists like acetylcholine, bradykinin, or ATP act on G-protein–coupled receptors leading to activation of phospholipase C–β, production of inositol 3,4,5 trisphosphate (IP3), and IP3-induced release of intracellular Ca2+. This rapid increase in Ca2+ is sustained by Ca2+-influx through store-operated channels (SOC). The increased Ca2+ then opens intermediate (IKiso) and/or small (sIKiso) conductance Ca2+-activated K+ channels, leading to endothelial membrane hyperpolarization. This hyperpolarization may activate KIR channels, effectively amplifying the change in membrane potential. Elevated extracellular K+ released from endothelial or smooth muscle K+ channels, or increases in shear-stress may also activate endothelial KIR channels and contribute to endothelial cell hyperpolarization. Endothelial cells are electrically coupled by gap junctions14 so that hyperpolarization can be conducted for long distances along the length of arterial endothelium, a process that may be enhanced by hyperpolarization-induced activation of KIR channels. In some arteries and arterioles, smooth muscle cells (VSM) are electrically coupled to endothelial cells through myoendothelial gap junctions14 such that endothelial hyperpolarization, per se, in the absence of chemical mediators, can lead to vasodilatation by closure of voltage-gated Ca2+ channels (VGCC).14 Agonist-induced increases in endothelial Ca2+ also leads to production of endothelium-derived vasodilators such as NO, prostacyclin (PGI2) and other vasodilator prostaglandins, and epoxides of arachidonic (EETs). All of these signals (hyperpolarization, NO, PGI2, EETs) are integrated by overlying smooth muscle cells to yield vasodilatation.
References


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