Potassium Ions as Vasodilators
Role of Inward Rectifier Potassium Channels

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Exterior potassium ions have long been known as mediators of vasodilation of several vascular beds, including the coronary and cerebral circulations. Indeed, potassium ions have been viewed as communicators of the metabolic state of the cells that surround blood vessels. For example, release of potassium ions from neurons is communicated through glial cells to regulate cerebral artery diameter. Recently, it has been suggested that the potassium ions from endothelial cells may signal smooth muscle to relax and, as such, may constitute an endothelial-derived hyperpolarizing factor.

Two targets of external potassium ions have been proposed: the Na/K ATPase and the inward rectifier potassium channel. An elevation of external potassium causes very different responses of these two molecular targets. The electrogenic Na/K ATPase is activated by external potassium with a half-activation constant of about 1 to 2 mmol/L and saturation above 5 mmol/L. Activation of the Na/K ATPase by elevating external potassium from nominally 0 to 5 mmol/L causes transient hyperpolarization and dilation; the transient nature presumably reflects the extrusion of sodium until a new steady state is reached. In contrast, elevation of external potassium causes a graded shift in the apparent voltage-dependence of the inward rectifier potassium channel conductance, which can lead to a maintained hyperpolarization and dilation. Unfortunately, the dissection of these pathways until recently has relied on two imperfect pharmacological probes: cardiotonic steroids, such as ouabain, and barium ions. Inhibition of the Na/K ATPase with ouabain leads to a membrane potential depolarization, an elevation in intracellular sodium and calcium, and several other changes downstream from these events. This complicates the interpretation of ouabain effects, unless it has no effect on potassium-induced hyperpolarization and dilations. Barium ions block inward rectifier potassium channels with a relatively high affinity of ~10 μmol/L at physiological membrane potentials. Nonetheless, barium ions block other ion channels at higher concentrations. These problems have been obviated by the use of inward rectifier knockout mice, which have been shown to lack potassium-induced dilations.

Much of the research on potassium-induced dilations has focused on the cerebral and coronary circulation. Small increases in circulating potassium ions in vivo dilate and increase cerebral flow. Recently, Chrissabolis et al demonstrated that cerebral artery dilations in vivo to elevated K+ in cerebral spinal fluid were Ba2+-sensitive and insensitive to ouabain, strongly supporting a role for inward rectifier potassium channels. In the cerebral vasculature, elevations in K+ ions increase with neuronal activity and during stresses such as cerebral hypoxia, ischemia, and hypoglycemia. K+-induced dilations have also been reported in coronary arteries. K+ ions are normally released from cardiac cells during increased workload and particularly under ischemia. In the kidney, elevated potassium (~10 mmol/L) or acute hyperkalemia have been shown to increase renal blood flow and glomerular filtration rate.

In a study in this issue of Circulation Research, Chilton and Loutzenhiser have explored the role of inward rectifier potassium channels in K+-induced dilations of rat renal afferent arterioles, using the hydronephrotic kidney model. This model permits visualization of the renal microvasculature under normal flow and pressure conditions. Loutzenhiser et al have taken this model one step further and developed a method for measuring stable membrane potentials while simultaneously measuring diameter of intact afferent arterioles in the intact kidney. In pressurized afferent arterioles, increasing [K+] from 5 to 15 mmol/L resulted in Ba2+-sensitive dilations. In the presence of the α-adrenoceptor blockers, K+-induced dilations were also abolished by chloroethylclonidine (CEC). CEC has been shown to inhibit native inwardly rectifying potassium channels (Kir) in skeletal muscle (rat flexor digitorium brevis) as well as Kir2.1 channels expressed in the MEL cell line. Neither the Kir ATP channel inhibitor glibenclamide nor ouabain inhibited K+-induced dilations in the afferent arteriole. Ba2+ depolarized and constricted afferent arterioles at low pressures, suggesting a role for Kir channels in regulating membrane potential. The Chilton and Loutzenhiser study, along with studies on the cerebral and coronary circulation, strongly supports the idea that the inward rectifier potassium channel, in particular the Kir2.1 subtype, is a molecular target for external potassium-induced vasodilation.

References

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