Potassium channels: physiological, pathological and protective roles

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Potassium channels play a crucial physiological role. Without their activity, cardiac life would cease. In disease states, potassium outflow is seen as harmful and associated with depolarization. Opening of one specific potassium channel, the K\textsubscript{ATP} channel, may however, be the final common path in the protective phenomenon of preconditioning. Of interest, several cardioprotective agents such as the opiates or the calcium blocker mibebradil, also appear to act via this channel. The antianginal agent, nifedipine, may also promote preconditioning, although this is a challenging concept to be proven in patients. 

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Potassium channels of this family set the resting membrane potential of primitive cells. This simple structure might first have come into existence to generate the resting membrane potential, probably with only two transmembrane helices (spans), thereby conserving ATP. When the beating heart emerged in the evolution of potassium channels, the inward rectifier potassium current IK\textsubscript{i} (also called IK\textsubscript{IR}), IK\textsubscript{ir}, Ik, or IRK, was the inward rectifier potassium current: Normally, the relationship between the voltage and current is a straight line (Ohm’s law). When a current can pass through the channel in both directions, but the flow in one direction is greater, then this selective process is called rectification. The K\textsubscript{i} channel rectifies in an inward direction when the voltage drops below the equilibrium potential for potassium (at about -90 mV). At a molecular level, the concept is that the inward current “unplugs” an internal divalent ion such as magnesium that would normally block the channel pore. Because of the marked deviation of the voltage-current relationship for this channel, the current is also called the anomalous rectifier. Outward rectification occurs when the major current flow is in the outward direction but voltage is more positive than zero. Thus, biologically, rectification of the K\textsubscript{i} channel can be achieved by plugging or unplugging by Mg\textsuperscript{2+} ions of the inner side of the pore.

Voltage-operated K\textsuperscript{+} channel, K\textsubscript{v} or Kv

This channel, also called the delayed rectifier (and including the rapid and slow components, K\textsubscript{R} and K\textsubscript{S}) conducts the current I\textsubscript{K} that physiologically makes a major contribution to repolarization. There is some resemblance to the sodium or calcium channel structure, but here the \(\alpha\)-subunit of each channel has only six helices in contrast to the twenty-four of the sodium or calcium channels. To make one single potassium pore that functions, four of the potassium-type \(\alpha\)-subunits must combine, so that as in the case of the Na\textsuperscript{+} or Ca\textsuperscript{2+} channel, there is one pore per 24 helices. The superfamily that includes this channel is sometimes called the Shaker family because the delayed rectifier was first cloned in a mut-
tand of the fruitfly, Drosophila. When this channel is genetically absent from the fruitfly, exposure to ether provokes spasms of muscular shaking.

**ATP-sensitive potassium channel**

Hypothetically, this channel evolved to conserve cell ATP during hypoxic or ischaemic damage, which would cause ATP to run down and thereby invoke irreversible damage. In general, this channel is very sensitive to inhibition by ATP and is firmly closed in physiological conditions when ATP is high. As ATP breaks down during ischaemia with formation of ADP and adenosine, opening of this K+ channel is promoted. This channel represents a hybrid between the K$_{r}$ superfamily and the totally different ABC (ATP-binding cassette) family. The latter provides two different inhibitory binding sites, one for the SURs (sulfonylureas, epitomized by the oral antidiabetic agent, glibenclamide) and the other for ATP. Because the channel is controlled by the binding of internal ATP to the ATP site, it is called the K$_{ATP}$ channel. The evolutionary function of the SUR binding site is at all not clear (how would the evolving heart cell know what the structure of an antidiabetic sulfonylurea drug be?)

There appears to be no physiological role for K$_{ATP}$ in cardiac myocytes. Pathophysiologically, one hypothesis is that, as ATP breaks down in response to severe ischaemia, the outward passage of K$^+$ ions and their accumulation on the outside of the cell causes loss of the normal membrane polarization, with a decreased contractile response and an induced state of inactivity or rest that conserves ATP.

The function of K$_{ATP}$ in vascular smooth muscle is much clearer. There, in response to the formation of adenosine, this channel opens and participates in coronary vasodilation. Adenosine formed during myocardial hypoxia or during vigorous work is thought to diffuse from the cardiac myocyte to the K$_{ATP}$ channel on vascular smooth muscle cells, to relieve the inhibition by ATP and to allow channel opening. The egress of potassium ions opening causes hyperpolarization that, in turn, leads to vasodilation by inactivation of the calcium channels. (This vasodilatory mechanism is distinct from the interaction of adenosine with K$_{ADC}$, although both mechanisms lead to hyperpolarization.)

The clinical implications of the inhibition K$_{ATP}$ by sulfonylureas relate to their use as oral agents in the therapy of maturity onset diabetes mellitus. These drugs, such as glibenclamide, inhibit K$_{ATP}$ and promote coronary vasoconstriction. They also lessen ischaemic loss of potassium and early ischaemic arrhythmias. They inhibit the protective phenomenon of preconditioning. Other drugs known as potassium channel openers, such as pinacidil, cromakalim, minoxidil, dazoxide, and the mixed nitrate-potassium opener nicorandil, all induce coronary dilation by promoting K$_{ATP}$ opening. By mechanisms not fully understood, these drugs protect ischaemic myocardial cells.

**Pathological role**

In ischaemia, it is not only the ATP-sensitive potassium channel that opens, but several other new channels may come into operation. A sodium-activated potassium current, responding to a rise in internal sodium, may become important in ischaemia, when internal sodium is known to increase. Its existence remains controversial. Likewise, the fatty acid-activated potassium channel also appears to respond to changes in ischaemia when there is a build-up of fatty acid metabolites.

**Protective role**

**Role of K$_{ATP}$ channel in preconditioning**

The mechanism of the protective effect of preconditioning is still speculative and controversial. A common view is that adenosine plays a role in the phenomenon, possibly being linked to activation of protein kinase C and thence to opening of the ATP-sensitive potassium channel. For example, adenosine A$_{1}$ receptor stimulation of rat ventricular myocytes activates the δ-protein kinase C isofrom [1]. Alternatively or additionally, there may be an increased activity of the inhibitory G-protein, G$_{i}$, which links the adenosine and opioid receptors to the ATP-sensitive potassium channel [2, 3]. Upregulation of G$_{i}$ would explain the protective effects of activation of those receptors coupled to it, such as adenosine A$_{1}$ and muscarinic M$_{2}$ receptors, because of greater inhibition of adenylate cyclase, and hence an indirect antiadrenergic effect. In addition, G$_{i}$ may mediate other potentially protective mechanisms, such as direct inhibition of L-calcium channels and activation of the K$_{ATP}$ channel [4].

**Preconditioning in patients**

Preconditioning is, therefore, an important phenomenon with probable clinical application because it invokes protection against postischaemic and other types of ischaemia-related impaired LV dysfunction. Although the clinical evidence for preconditioning is not yet firm, there is suggestive evidence that it occurs in humans [5]. Patients with effort angina who have had one attack may be protected from subsequent attacks as in "warm-up" angina. Those undergoing coronary angioplasty have more severe features of ischaemia, such a potassium release and ST-segment elevation on the ECG, on the first when compared with subsequent balloon inflations. Patients with pre-infarction angina may suffer from a less severe infarct than those thought to undergo sudden coronary occlusion without the opportunity for preconditioning [6]. In contrast, experimental datas suggest that patients with multiple short-lived attacks of ischaemia might become tolerant to the protection conferred by preconditioning [7].

Thus, not only are there several stimuli to the preconditioned state, but also there are several potential mechanisms, and the consequences are multiple. Hence the possibility must be considered that preconditioning occurs in any state of repetitive ischaemia, and also in patients.

**The K$_{ATP}$ channel as the final common protective path in preconditioning**

There is increasing evidence that the K$_{ATP}$ channel mediates cardiac protection that is more widespread than anticipated, in addition to its proposed role as the end point of the complex signaling paths that operate in preconditioning. For example, this channel mediates the pharmacological preconditioning achieved by opiates compounds [3]. But this channel may also mediate protection that is not part of the classical preconditioning paradigm. An example is that the calcium channel blocker, mibefradil, mediates its protective effect on infarct size in pigs by a process blocked by glibenclamide, and therefore involving the K$_{ATP}$ channel [8]. Clinically, there as yet are no drugs specifically exerting their protective effect by acting on the K$_{ATP}$ channel. The antiischaemic agent nicorandil does have a mixed action, partially as a nitrate, and partially as an opener of the K$_{ATP}$ channel. Of interest, nicorandil exerted an anti-ischaemic and antiarrhythmic effect when added to beta-blockade and diltiazem in the treatment of unstable angina [9]. More investigations concerning the possible preconditioning effect of this drug are warranted.
Acknowledgements

For further details on the physiological role of potassium channels, readers may refer to Chapter 4 of my book, The Heart, Physiology, from Cell to Circulation, Lippincott Raven, 1999. I wish to thank Professor Derek Yellon, London, for many stimulating conversations.

References

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