Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 1999; 2 (1), 5-7

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Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

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 $K_{(ATP)}$ 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 mibefradil, also appear to act via this channel. The antianginal agent, nicorandil, may also promote preconditioning, although this is a challenging concept to be proven in patients. *J Clin Basic Cardiol 1999; 2: 5–7.*

Potassium channels must function normally for life to continue. Of the many potassium channels, I wish to select three, each potentially life-saving in a different way. First, without the inward rectifier potassium current IK_1 (also called IK_{ir}), there would be no resting membrane potential, no polarization of cells, no depolarization, and no cardiac contraction. Second, without the delayed rectifier current, IK (also called IK_v), there would be no recovery of the cardiac action potential after depolarization, so that the heart cells would die in hypercontracture as the calcium ions continued to pour in. Third, the ATP-sensitive potassium channel is the major protective potassium channel, sensitive to ATP-depletion. By opening, it protects the heart cells in a still poorly understood way from the effects of hypoxia and ischaemia. These three major potassium channels stem from two distinct molecular families, namely the inward rectifier family that includes the $K_{(ATP)}$ channel, and the voltage-gated (or voltage-operated) family of channels. Without these families of potassium currents, life would cease.

Physiological role

Evolution of potassium channels

Seen from an evolutionary perspective, a very simple K^+ channel, probably with only two transmembrane helices (spans), might first have come into existence to generate the resting membrane potential of primitive cells. This simple structure is now called the inward rectifier, K_{ir}. The other major member of this family, the ATP-sensitive K^+ channel, $K_{(ATP)}$, supposedly evolved to stop damaged heart cells from contracting, thereby conserving ATP. When the beating heart emerged in evolution, the K_v superfamily came into existence. Members of the K_{ir} family also evolved into a third major branch of the superfamily that includes K_{ACh} and K_{ADO} that respond respectively to acetylcholine and to adenosine, in each case acting to decrease the heart rate, another protective event.

To achieve a functioning potassium channel pore requires the combination of multiple subunits, that is either 4 subunits each of 6 spans or the combination of four units each of only 2 spans. Such variable combinations mean that a great molecular diversity of potassium channels is possible.

The inward rectifier superfamily, K_{ir}

Potassium channels of this family set the resting membrane potential of cardiac myocytes. Structurally, this type of channel is an extremely simple channel with a basis of only two transmembrane helices and one pore. To achieve a functioning potassium channel pore requires the combination of multiple subunits, that is the combination of four units each of only 2 spans. K_{ir} passes an *outward current* when the membrane potential is above the potassium equilibrium potential (E_k) to contribute to the repolarization phase of the action potential and thereby to help end the action potential, thereby regaining the resting membrane potential. Conversely, this same channel potentially passes a large *inward* K^+ current, when the cell membrane is hyperpolarized (ie, when the resting membrane potential is below -85 mV) and this inward current helps to maintain the high internal K^+ activity and hence the membrane polarity. The unusual nature of the current flow, which is much larger in one direction, has given rise to the name *anomalous rectifier*.

Rectification of 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_{ir} 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, hypothetically, rectification of the K_{ir} channel can be achieved by plugging or unplugging by Mg^{2+} ions of the inner side of the pore.

Voltage-operated K^+ channel, K_v or K

This channel, also called the delayed rectifier (and including the rapid and slow components, K_r and K_s) conducts the current I_k that physiologically makes a major contribution to repolarization. There is some resemblance to the sodium or calcium channel structure, but here the α-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 α-subunits must combine, so that as in the case of the Na^+ or Ca^{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 mu-

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tant 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_{ir} superfamily and the totally different ABC (ATP-binding cassette) family. The latter provides two different inhibitory binding sites, one for the SURs (*s*ulfonyl*ur*eas, 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 could 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_{ADO}, 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, diaxozide, 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 isoform [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 opiate 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 antianginal 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.

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