PERSPECTIVES IN PHYSIOLOGY

Coming closer: structure and function of calcium-activated K^+ channels in coronary arteries

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Both the elucidation of the molecular structure of various K^+ channel proteins and the electrophysiological characterization of potassium channels in various tissues are making rapid progress. However, in view of the diversity of K^+ channels, different subtypes often being expressed in the same cell, it is still very difficult to correlate the properties of native channels with the properties of channels found by heterologous expression of K^+ channel clones in *Xenopus* oocytes or mammalian cell lines. The study of Tanaka *et al.* (1997) published in this issue of *The Journal of Physiology* tries to correlate the properties of cloned maxi K_{Ca} channels (large-conductance calcium-activated potassium channels, BK channels) with the properties of maxi K_{Ca} channels in human coronary smooth muscle cells.

Calcium-activated K^+ channels are probably the most abundant type of K^+ channel in vascular smooth muscle. Nevertheless, their function has long remained elusive. In general, hyperpolarization in vascular smooth muscle appears to be associated with vasodilatation, and depolarization appears to be associated with vasoconstriction (Nelson & Quayle, 1995). Thus, activation of K_{Ca} channels would be expected to be associated with vasodilatation under conditions in which intracellular calcium is raised. Elevation of transmural pressure causes an elevation of free intracellular calcium in resistance arteries, thereby increasing the tone of smooth muscle cells, a phenomenon known as 'myogenic tone'. It has been proposed that one of the functions of K_{Ca} channels is to limit myogenic tone (Brayden & Nelson, 1992) and thus prevent damage to the tissues during near-maximum constriction of arterioles. This hypothesis was based largely on pharmacological evidence: charybdotoxin and iberiotoxin, which in vascular smooth muscle selectively block K_{Ca} channels, caused depolarization and constriction of pressurized coronary and cerebral resistance arteries.

The recent discovery of calcium sparks in vascular smooth muscle (Nelson *et al.* 1995) has added another facet to the elucidation of K_{Ca} channel function. Calcium sparks are rapid local increases in intracellular calcium resulting from activation of ryanodine-sensitive calcium-release channels. During such sparks high local calcium concentrations can be reached that may activate a group of maxi K_{Ca} channels (of the order of 10–20). The local activation of maxi K_{Ca} channels can produce hyperpolarization of the entire cell because the passive electrical properties are such that smooth muscle cells are isopotential under physiological conditions. The 'global' hyperpolarization of the cell results in a decrease of the open-state probability of L-type calcium channels and in a subsequent decrease in global myoplasmic calcium (Nelson *et al.* 1995).

The pore-forming α subunit of the maxi K_{Ca} channel possesses ten hydrophobic domains, the first six domains resembling voltage activated K^+ channels and the four additional N-terminal domains being related to calcium binding (Butler *et al.* 1993). When α subunits of maxi K_{Ca} channels were expressed in oocytes or CHO cells they showed a much lower Ca^{2+} sensitivity than native vascular maxi K_{Ca} channels. However, co-expression of the α subunits with a β subunit derived from smooth muscle caused a large increase in Ca^{2+} sensitivity (McCobb *et al.* 1995). The macroscopic current attributable to maxi K_{Ca} channels was shown to be activated by dehydrosoyasaponin (DHS-I) only if α and β subunits were co-expressed.

Tanaka *et al.* (1997) have now tried to correlate the recent data obtained by heterologous expression of maxi K_{Ca} channels with patch clamp recordings from freshly dissociated human coronary smooth muscle cells from patients who had undergone heart transplant. They compared the calcium sensitivity of native channels with the calcium sensitivity of heterologously expressed channels, and used DHS-I as a probe to test for subunit composition. Their elegant electrophysiological study shows that the majority of the maxi K_{Ca} channels in native coronary smooth muscle were half-activated near -85 mV in the presence of 18 μM intracellular Ca^{2+}. A Ca^{2+} concentration of 1·2 μM was sufficient to produce a measurable increase in the open-state probability of the channels in inside-out patches. DHS-I shifted the activation curve of macroscopic K_{Ca} currents to more negative potentials. All these observations in freshly isolated smooth muscle cells are consistent with the properties of coupled α and β subunits as recorded in heterologous expression systems.

The work of Tanaka *et al.* (1997) suggests that, during calcium sparks, the open-state probability of maxi K_{Ca} channels in coronary smooth muscle cells might be sufficiently elevated to cause a hyperpolarization. Simultaneously global Ca^{2+} is expected to fall because the open-state probability of voltage-dependent Ca^{2+} channels decreases, thereby causing relaxation. Thus intracellular Ca^{2+} could transmit two different signals, hyperpolarization and relaxation, simultaneously via 'amplitude modulation' (Berridge, 1997). The electrical coupling between arterial smooth muscle cells would then average out membrane potential fluctuations resulting from activation of maxi K_{Ca} channel currents. In this way, local calcium sparks could cause a smooth and spatially homogeneous dilatation of coronary arterioles or conduit arteries.

Future studies will have to show what the local Ca^{2+} concentration is at the actual Ca^{2+} binding site of the channels during 'spontaneous' Ca^{2+} release from neighbouring ryanodine receptors and to what extent this alters the open-state probability of K_{Ca} channels at physiological membrane potentials. Despite these missing pieces of information, the work of Tanaka *et al.* (1997) represents the first successful attempt to correlate the properties of a cloned K^+ channel in smooth muscle with the properties of the native channel. Thus this study brings us much closer to understanding the function of maxi K_{Ca} channels *in vivo*.

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