KCNQ Channels and Novel Insights Into Coronary Perfusion

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See related article, pp 1090–1097

*K*7 (KCNQ) voltage-gated potassium channels are encoded by the KCNQ gene family, many of which display highly restricted and distinct tissue distribution. Cloning experiments have identified 5 KCNQ genes (KCNQ1–5). Mutations in 4 of the 5 genes of the KCNQ gene family have been associated with inherited diseases. KCNQ1 mutations cause cardiac arrhythmia in long QT syndrome with or without deafness. KCNQ2 and KCNQ3 mutations cause benign familial neonatal seizures and peripheral nerve hyperexcitability. Mutations in KCNQ4 underlie congenital deafness and modulate cutaneous touch sensitivity in man. No human disease has been related to KCNQ5 until now, KCNQ1, 3, 4, and 5 gene products are widely expressed in systemic arteries with KCNQ 4 and 5 being predominant. Current data suggest important roles for K*7* family in systemic peripheral arteries, namely myogenic response and vasoregulation by vasopressin, β-adrenoceptors, hydrogen sulfide, and perivascular adipose tissue.

In this current issue, Khanamiri et al have examined the possible role of K*7* channels in the rat coronary circulation. They document expression of KCNQ and their known accessory KCNE1–5 subunits. Their study relied on pharmacological modulators of KCNQ channels in isometric tension studies of isolated coronary arteries and Langendorff-perfused hearts to explore a possible role of KCNQ channels in coronary blood flow at rest and in response to ischemia. Of interest was the observation that vasodilatory effects of a key mediator of coronary ischemic vasodilation, namely adenosine, are inhibited by K*7* blockers. The results suggest that adenosine through adenosine A2 receptors and cAMP protein pathway activates K*7* channels (Figure). This is the first time that this signaling pathway has been observed in vascular smooth muscle. Of note, vasorelaxant effects of K*7*,7 to 7.5 activators were absent in coronary arteries isolated from spontaneously hypertensive rats, consistent with lower expression of K*7* as being responsible for coronary perfusion and restoration of cardiac reperfusion after transient coronary occlusion. The results suggest that K*7*,4 becomes dysfunctional in coronary circulation because 4-aminopyridine–sensitive K*7* channels are considered to play the most central role in regulating coronary blood flow (Figure) and these channels are reported to be involved in resting vascular tone, as well as endothelium-dependent, ischemic, and metabolic coronary vasodilation.

Admittedly, work with pharmacological tools is fraught with confounders. Pharmacological modulators of K*7* channels may have side effects on non-KCNQ K*7* channels. Khanamiri et al tried to rule out such possibilities using a large repertoire of structurally different K*7* channel blockers and agonists. Experiments with 4-aminopyridine were performed to rule out nonspecific block of non-KCNQ K*7* channels. Nonetheless, it was surprising that prolonged infusion with XE-991 or linopirdine (K*7* blockers) to the isolated hearts only resulted in a very modest reduction of coronary blood flow. Based on previous data and current views, one would have expected a much more profound reduction in blood flow if KCNQ channels had the proposed prominent role in the contractile state of coronary vascular smooth muscle.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.113.01869

Figure. K*7* channels are KCNQ gene products and were also reported to behave as voltage-gated potassium channels in vascular smooth muscle cells. Schematic diagram of the channel in a coronary artery smooth muscle cell (CASMC) is prepared according to Dicker and Tune. The Na+/K+-ATPase accumulates intracellular K+, providing a large chemical gradient for diffusion of K+ through open (K*K*, K*ATP, and BK) channels. Efflux of K+ largely determines membrane potential E*m* which regulates the steady-state open probability (P*) of L-type Ca*2+.2 Ca*2+ channels. The level of free global intracellular Ca*2+ determines the contractile state of coronary vascular smooth muscle.
regulation of coronary artery function (Figure). It is unclear whether 10 \( \mu \)mol/L linopirdine+3 \( \mu \)mol/L XE-991 are sufficient to inhibit a significant proportion of K\(_{7.4}\) channels in coronary arteries. The role of the known accessory KCN\(E\)1–5 subunits is unclear. Recent data implicate that unsaturated heteromultimeric (KCNQ)\(_1\)4(KCNE)\(_1\) channels are pharmacologically distinct from KCNE-saturated KCNQ\(1\)–KCNE\(1\) channels. The present study supports a central role of KCNQ channels in the regulation of coronary blood flow. However, given issues with drug specificity and possible heteromultimeric channel complexes, it will be critical to incorporate appropriate genetic models to establish firmly the roles of KCNQ channels in vascular function. Thus, we could find out which K\(_{7.4}\)/KCNE channels are involved.

**Sources of Funding**

Dr Gollasch’s research is supported by the Deutsche Forschungsgemeinschaft.

**Disclosures**

None.

**References**

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Hypertension. 2013;62:1011-1012; originally published online September 30, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.01869
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/62/6/1011

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