KCNQ Channels and Novel Insights Into Coronary Perfusion

Maik Gollasch

See related article, pp 1090–1097

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v7 (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 KCNQ family in systemic peripheral circulation because 4-aminopyridine–sensitive Kv 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 Kv7 channels may have side effects on non-KCNQ Kv channels. Khanamiri et al tried to rule out such possibilities using a large repertoire of structurally different Kv7 channel blockers and agonists. Experiments with 4-aminopyridine were performed to rule out nonspecific block of non-KCNQ Kv channels. Nonetheless, it was surprising that prolonged infusion with XE-991 or linopirdine (Kv7 blockers) to the isolated hearts only resulted in a very modest reduction of coronary 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 coronary circulation in hypertension. This work supports a growing paradigm shift in the role of Kv7 channels in coronary circulation because 4-aminopyridine–sensitive Kv7 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.

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From the Medical Clinic for Nephrology and Internal Intensive Care, Charité Campus Virchow Klinikum, Experimental and Clinical Research Center (ECRC), Berlin, Germany.

Correspondence to Maik Gollasch, Medical Clinic for Nephrology and Internal Intensive Care, Charité Campus Virchow Klinikum, Experimental and Clinical Research Center (ECRC), Augustenburger Platz 1, 13353 Berlin, Germany. E-mail maik.gollasch@charite.de

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

Figure. Kv7 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 Dick and Tune. The Na+/K+-ATPase accumulates intracellular K+, providing a large chemical gradient for diffusion of K+ through open (Kv7, Kv8, and BK) channels. Efflux of K+ largely determines membrane potential E膜, which regulates the steady-state open probability (P开门) of L-type Ca2+ channels. The level of free global intracellular Ca2+ determines the contractile state of coronary vascular smooth muscle.
regulation of coronary artery function (Figure). It is unclear whether 10 µmol/L linopirdine+3 µmol/L XE-991 are sufficient to inhibit a significant proportion of Kv7.4 channels in coronary arteries. The role of the known accessory KCNE1–5 subunits is unclear. Recent data implicate that unsaturated heteromultimeric (KCNQ1)4(KCNE1)n channels are pharmacologically distinct from KCNE-saturated KCNQ1–KCNE1 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 Kv7/KCNE channels are involved.

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

Disclosures
None.

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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

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World Wide Web at:
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