KCNQ7 (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.

In this current issue, Khanamiri et al have examined the possible role of KCNQ7 channels in the rat coronary circulation. They showed that KCNQ7 expression in systemic arterioles of the rat coronary circulation in hypertension. The authors conclude that KCNQ7 channels play 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.

Admittedly, work with pharmacological tools is fraught with confounders. Pharmacological modulators of KCNQ7 channels may have side effects on non-KCNQ KCN channels. Khanamiri et al tried to rule out such possibilities using a large repertoire of structurally different KCNQ7 channel blockers and agonists. Experiments with 4-aminopyridine were performed to rule out nonspecific block of non-KCNQ KCN channels. Nonetheless, it was surprising that prolonged infusion with XE-991 or linopirdine (KCNQ blockers) to the isolated coronary arteries and Langendorff-perfused hearts to explore a possible role of KCNQ7 channels in coronary blood flow at rest and in response to ischemia. It seems that the observation that vasodilatory effects of a key mediator of coronary ischemic vasodilation, namely adenosine, are inhibited by KCNQ7 blockers. The results suggest that adenosine through adenosine A2 receptors and Ca2+ entry may have a role in coronary blood flow. Based on previous data and current views, one would have expected a much more profound reduction in blood flow if KCNQ7 channels had the proposed prominent role in the

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

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KCNQ Channels and Novel Insights Into Coronary Perfusion

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See related article, pp 1090–1097

Figure. KCNQ7 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 (CASM) 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 (KCNQ, BK, and Kv1.5) channels. Efflux of K+ largely determines membrane potential E<sub>m</sub>, which regulates the steady-state open probability (P<sub>o</sub>) of L-type Ca<sub>2+</sub> Ca<sub>2+</sub>-channels. The level of free global intracellular Ca<sub>2+</sub> 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.

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