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 KCNQ4 mutations cause cardiac arrhythmia in long QT syndrome with or without deafness. Mutations in KCNQ3 and KCNQ4 cause familial neonatal seizures and peripheral nerve hyperexcitability. Mutations in KCNQ5 until now.

KCNQ5 gene products are widely expressed in systemic arteries, namely myogenic response and vasoregulation by vasopressin, β-adrenoceptors, hydrogen sulfide, and perivascular adipose tissue. Current data suggest important roles for KCNQ7 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 KCNQ7 channels in the rat coronary circulation. They demonstrated 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 KCNQ7 blockers. The results suggest that adenosine through adenosine A2 receptors and cAMP protein pathway activates KCNQ7 channels (Figure). This is the first time that this signaling pathway has been observed in vascular smooth muscle. Of note, vasorelaxant effects of KCNQ7.2 to 7.5 activators were absent in coronary arteries isolated from spontaneously hypertensive rats, consistent with lower expression of KCNQ7.4 protein, reduced vasodilatory effects of adenosine, and attenuated level of reactive hyperemia in hearts from spontaneously hypertensive rats. The authors conclude that KCNQ7 channels provide a crucial functional end point for adenosine-mediated signaling in coronary arteries. To my knowledge, this study is the first example of a faulty (or absent) KCNQ channel(s) (KCNQ7.4) as being responsible for coronary perfusion and restoration of cardiac reperfusion after transient coronary occlusion. The results suggest that KCNQ7.4 becomes dysfunctional in the coronary circulation in hypertension. This work supports a growing paradigm shift in the role of KCNQ7 channels in coronary circulation because 4-aminopyridine–sensitive KCNQ7 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 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 blockers and agonists. Experiments with 4-aminopyridine were performed to rule out nonspecific block of non-KCNQ KC7 channels. Nonetheless, it was surprising that prolonged infusion with XE-991 or linopirdine (KCNQ7 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 KCNQ7 channels had the proposed prominent role in the coronary circulation because 4-aminopyridine–sensitive KCN7 channels largely determine membrane potential, which regulates the steady-state open probability (P0) of L-type Ca2+2 Ca2+ channels. Efflux of K+ through open (Kv, KATP, and BK) channels. Efflux of K+ through open (Kv, KATP, and BK) channels.

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 (CASMOC) 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 (Kv, KATP, and BK) channels. Efflux of K+ largely determines membrane potential, which regulates the steady-state open probability (P0) 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 K<sub>7.4</sub> 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 K<sub>V7</sub>/KCNE channels are involved.

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**Disclosures**

None.

**References**