Expression and function of Kv7.4 potassium channels in cardiac cell mitochondria

V. Calderone[1], L. Testai[1], V. Barrese[2], M.V. Soldovieri[3], P. Ambrosino[3], A. Martelli[1], M.C. Breschi[1], M. Taglialatela[2,3]

[1] Dipartimento di Farmacia, Università di Pisa, via Bonanno, 6, I-56126 Pisa,
[2] Sezione di Farmacologia, Dipartimento di Neuroscienze, Università di Napoli 'Federico II'
[3] Dipartimento di Medicina e di Scienze della Salute, Università del Molise

Mitochondrial membrane potential crucially regulates cell fate towards death or survival during physiological or pathophysiological states such as ischemia/reperfusion injuries. Mitochondrial membrane potential control in eukaryotes is achieved through the expression of several ion channels in the inner mitochondrial membrane. Among potassium channels, the presence of ATP-sensitive (mitoKATP) and large-conductance calcium-activated potassium channels (mitoBKCa), whose activation confers an increased resistance against cardiomyocytes ischemia/reperfusion injury, is widely recognized in cardiac mitochondria (Szabo et al., 2012; Ardehali and O'Rourke 2005; Xu et al., 2002). These mitochondrial channels are viewed as attracting pharmacological targets for cardioprotective strategies (Calderone et al., 2010; Kang et al., 2007). Other potassium channel types, such as the Kv1.3 and TASK-3, have been also described in mitochondria of non-cardiac cells (Szabo et al., 2012). The Kv7 subfamily of voltage-gated potassium channels (Kv7.1-Kv7.5), plays a key pathophysiological role in controlling excitability of cardiac, neuronal, and sensory cells. Mutations in four of five Kv7 genes are responsible for cardiac arrhythmias (Kv7.1), epilepsy (Kv7.2 and Kv7.3), or deafness (Kv7.4) (Soldovieri et al., 2011). Kv7 channels are endowed with unique electrophysiological and pharmacological characteristics; in fact, they are activated at very low voltages, and their opening (except for Kv7.1) is facilitated by selective Kv7-activators such as retigabine and flupirtine.

In the present study, the possible presence of Kv7 potassium channels in heart mitochondria has been investigated. Potentiometric recordings in isolated rat heart mitochondria showed that retigabine (1-30 μM) and flupirtine (1-30 μM) evoked concentration-dependent depolarizing responses and inhibited mitochondrial calcium uptake. Both these effects were antagonized by the selective Kv7-blocker XE991 (10 μM). Consistently, both Kv7-activators promoted XE991-sensitive trans-membrane influx of thallium (a potassium-mimetic cation) into the mitochondrial matrix. Western-blot experiments using antibodies against each Kv7 subunit, revealed the selective expression of Kv7.4 in isolated rat heart mitochondria. Finally, confocal immunocytochemical experiments in cultured H9c2 rodent cardiomyoblasts revealed a prominent expression of Kv7.4 subunits in mitochondria, as anti-Kv7.4 antibodies immunolabelling strongly colocalized with the fluorescent signal of the mitochondrion-selective probe MitoTracker® Red FM. Future investigations will be aimed to identify the biological relevance, the possible pathophysiological roles, and the pharmacological implications of this novel class of mitochondrial ion channels.

Ardehali and O'Rourke (2005) J Mol Cell Cardiol. 39, 7–16.
Calderone et al., (2010) Biochem Pharmacol. 79, 39–47.
Kang et al., (2007) Am J Physiol Heart Circ Physiol. 293, H307–H313.
Soldovieri et al., (2012) Physiology. 26, 365–376.
Szabò et al., (2012) Pflugers Arch-Eur J Physiol. 463, 231–246.
Xu et al., (2002) Science. 298, 1029–1033.