Kv7.4 channels in rat cardiac mitochondria: new targets for cardioprotection

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Many endogenous mechanisms of cardioprotection, such as the ischemic pre-conditioning, are often mediated by the activity of mitochondrial potassium channels (mitoKCs). Thus, the identification and the molecular characterization of the mitoKCs expressed in the heart mitochondria is a compelling issue in cardiovascular pharmacology (Testai et al., 2014). The presence of ATP-sensitive and of calcium-activated KCs in cardiac mitochondria is well recognized (Inoue et al., 1991; Xu et al., 2002), and their role in cardioprotection is widely accepted. On the other hand, sarcolemmal KCNQ KCs (Kv7) are almost ubiquitously expressed and play pivotal roles in controlling neuronal excitability, smooth and skeletal muscle activity and myocardial repolarization (Soldovieri et al., 2011). However, subcellular localization of Kv7 channels and their role in ischemia/reperfusion injury is unknown.
In the present work, the expression and function of cardiac mitochondrial Kv7 channels have been investigated, and their possible cardioprotective role has been evaluated in experimental models of myocardial ischemia/reperfusion injury.
Expression of Kv7, (in particular, Kv7.1 and Kv7.4 subtypes) transcripts was clearly found in rat heart tissue by qPCR. Western-blot experiments detected the selective presence of Kv7.4 subunits in heart mitochondrial fractions. Immunofluorescence experiments in freshly isolated cardiac cells, rat H9c2 cardiomyoblasts, and cardiac slices co-localized Kv7.4 subunits with mitochondrial markers. Kv7.4 localization in cardiac mitochondria was also confirmed by electron microscopy. In isolated rat heart mitochondria, retigabine (1-30 mM) and flupirtine (30 mM), activators of Kv7.4, increased trans-membrane influx of the K^+-mimetic cation thallium, depolarized the membrane potential, and inhibited calcium uptake. These effects were antagonized by the Kv7-selective blocker XE991. Retigabine improved the cell viability in H9c2 cardiomyoblasts exposed to anoxia/reoxygenation and largely restored the functional changes and the tissue injury in Langendorff- perfused rat hearts submitted to global ischemia/reperfusion.
In conclusion, this study demonstrated that Kv7.4 channels are present and functional in cardiac mitochondria; their activation exerts a cardioprotective role, making them viable therapeutic targets against ischemia-reperfusion myocardial injury.

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