Pharmacological modulation of TRPV1, a cation leak channel in mouse cardiomyocytes

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The sarcoplasmic reticulum (SR) calcium homeostasis is due to a dynamic balance between the capture of the cytosolic calcium by calcium pumps such as SERCA (Sarco Endoplasmic Reticulum Calcium ATPase) and calcium release, actively across calcium channels such as IP3 (Inositol Tri-phosphate) and ryanodine receptors, or passively via calcium leak channels.

Few data are available concerning the functional characterization of leak channels in the SR. These channels are involved in the regulation of the reticular calcium concentration as well as in the exchange of calcium between SR and other intracellular organelles. Therefore, their characterization is important for a better understanding of the physiology of the cells.

Recently, we have demonstrated that TRPV1 (Transient Receptor Potential Vanilloid 1), a cationic channel, is a functional calcium leak channel on the SR of mouse skeletal muscle cells. TRPV1 is activated by acidosis, high temperature (>42°C), and by pharmacological molecules such as capsaicin, resiniferatoxain and capsazepine.

We are pursuing our investigation of these channels in C57Bl6 mouse cardiomyocytes.

Our preliminary results show that TRPV1 is active in mice cardiomyocytes as a calcium leak channel after stimulation or inhibition using pharmacological molecules.

These data were confirmed by using a genetic approach: the C57Bl6 KO mice for TRPV1 channel.

Lately, reducing cardiac injuries after ischemia reperfusion where calcium dynamics play a crucial role became a major interest. Therefore, the modulation of the TRPV1 calcium leak channel might be a new approach in cardiology.

Discussion:

The detection of a new type of calcium leak channel might have potential therapeutic impacts in various therapies, such as heart failure, diabetes, and muscular dystrophies.

Conclusion:

We show that the deficiency of the MR expressed in smooth muscle cells protects against the renal injury induced by IR. Our data provides further evidence to support the use MR antagonists as a novel therapeutic approach to prevent acute and chronic consequences of renal IR.

Cardioprotection against ischemia-reperfusion injury by heart rate control

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Background:

Acute myocardial infarction (AMI) is a major cause of mortality worldwide. Early reperfusion is the only treatment recommended to reduce infarct size. However, reperfusion induces also deleterious secondary effects called ischemia-reperfusion (IR) injury due to irreversible apoptotic death of cardiomyocytes. Most ischemic episodes are triggered by an increase in heart rate that induces an imbalance between myocardial oxygen delivery and consumption. The BEAUTIFUL clinical trial has demonstrated that moderate heart rate reduction diminishes the frequency of AMI episodes in patients with stable coronary artery disease having increased heart rate at rest. The HCN-mediated If current and the Cav1.3-mediated L-type Ca2+ currents play important roles in the generation of automaticity and heart rate, therefore they are interesting targets for selective control of heart rate and cardioprotection during AMI. The aim of this study was to investigate if Cav1.3 channels could be a putative target to reduce infarct size.

Methods:

Anesthetized C57BL/6J, Cav1.3-/- and Girk4-/- mice were subjected to a surgical protocol of myocardial IR (40min ischemia-60 min reperfusion). Heart rate was measured with a one-lead surface ECG recording, and infarct size with triphenyl tetrazolium chloride staining.

Results:

Selective heart rate decrease (26%) in an in vivo mouse model of AMI is associated with reduced IR injury. Ibradidine administration before ischemia significantly reduced infarct size (~33%). Cav1.3-/- mice presented reduced infarct size (~30%) compared to WT mice. In addition, Girk4-/- mice, a genetic model of moderate tachycardia (10%) displayed increased infarct size (+30%) compared to control mice.

Conclusions:

These results show a direct relationship between heart rate and IR injury. Heart rate reduction by inhibition of Cav1.3 channels constitutes a promising strategy to reduce infarct size.