**Compartmentalized Regulations of Ion Channels in the Heart**

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The rate and force of contraction of the heart are precisely controlled by compartmentalized regulation of cardiac ion channels which determine electrical activities. It has been known that modulation of cardiac ion channels, which is caused by drug-administration, sympathetic nervous system stimulation and gender difference, can increase risks of lethal arrhythmias in carriers of inherited disease mutations. These modulations are thought to be involved also in common heart arrhythmias. Because many signaling molecules are localized within single cells, an understanding of the molecular basis of compartmentalized regulation of cardiac channels is a key for understanding and treating the lethal arrhythmias.

I here introduce our previous research and recent progress on molecular mechanisms of compartmentalized regulation of cardiac ion channels via drugs, cAMP and nitric oxide (NO). First, local bindings of channel blockers are investigated to understand pharmacological effects on the L-type $Ca^{2+}$ ($I_{Ca,L}$) channel and the $I_{Ks}$ channel. Next, we found that the $I_{Ks}$ channel, a major contributor to cardiac repolarization, forms a macromolecular complex with the targeting protein AKAP7 (Yotiao) to up-regulate the $I_{Ks}$ activity upon cAMP-stimulation. The complex involves in increased risk of fatal arrhythmias in the face of sympathetic nervous system activity. Third, we have demonstrated that NO-production in the heart via a non-genomic action of sex hormones causes $I_{Ks}$-enhancement and $I_{Ca,L}$-suppression, and the regulation may have a major impact on sex-related difference in QT intervals and susceptibility to drug-induced arrhythmias. Localized regulation of the both channels by NO will be discussed regarding to cGMP-dependency.