Ryanodine receptor Ca^{2+} release channels and cardiac arrhythmia

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The type 2 ryanodine receptor (RyR2) is a Ca^{2+} release channel on the endoplasmic reticulum (ER) and plays a pivotal role in E-C coupling in the heart. Mutations in RyR2 have been linked to various types of cardiac arrhythmias such as catecholaminergic polymorphic ventricular tachycardia (CPVT), idiopathic ventricular fibrillation (IVF), long QT syndrome (LQTS), and so on. These mutations are supposed to develop arrhythmia via abnormal Ca^{2+} signaling in cardiac cells. However, the underlying cellular mechanisms are largely unclear, and hence the effective therapies for them remain to be established. To address these issues, we have developed an efficient approach for functional evaluation of mutant RyR2s by measurements of cytoplasmic and ER $[\text{Ca}^{2+}]$ and Ca^{2+} dependent Ca^{2+} release activity by $[^3\text{H}]$ ryanodine binding assay using HEK293 expression system (Murayama et al, Human Mut., 2016, Uehara et al. J. Gen. Physiol., 2017, Fujii et al. Heart Rhythm, 2017). We have found that all CPVT-related mutations exhibit gain-of-function (GOF) phenotypes whereas other IVF and LQTS-related mutations include both GOF and loss-of-function (LOF) phenotypes. In this presentation, I will summarize functional properties of RyR2 mutants related to a variety of cardiac arrhythmias, and show impact of them on Ca^{2+} signaling in cultured cardiomyocytes expressing mutant RyRs. Furthermore, as an attempt to develop therapies for RyR2-related arrhythmias, I will show the effects of RyR2-specific inhibitors, which were recently discovered by our high-throughput screening approach, on Ca^{2+} homeostasis in cardiac and non-cardiac cells expressing mutant RyR2s.