Abnormal RyR2 in arrhythmogenic disorders and CICR

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Ca^{2+} induced Ca^{2+} release (CICR) via ryanodine receptor 2 (RyR2) plays a central role in E-C coupling in cardiac cells, i.e., Ca^{2+} influx via L-type Ca^{2+} channels during action potential (AP) activates RyR2 to release Ca^{2+} from the ER and causes muscle contractions. Many arrhythmogenic mutations in RyR2 are reported to increase AP-independent spontaneous Ca^{2+} release from ER that often lead to arrhythmia. Two explanations have been proposed for the increased propensity of spontaneous Ca^{2+} release: (1) CPVT mutations increase the cytoplasmic Ca^{2+} sensitivity of RyR2 to enhance CICR, or (2) mutations decrease threshold for store-overload induced Ca^{2+} release (SOICR) by reducing luminal Ca^{2+} sensitivity of RyR2. To understand the underlying mechanism for the increased spontaneous Ca^{2+} release by the mutations, we performed quantitative evaluation of CICR activity and cytoplasmic and ER Ca^{2+} signals in HEK293 cells expressing mutant RyR2s. Furthermore, the effects of RyR2 inhibitors, which had been found by recently established high-throughput screening method, were examined on Ca^{2+} signals in RyR2-HEK cells and cardiomyocytes from adult mice. Our results indicate that CICR plays critical role in generation of spontaneous Ca^{2+} release and that regulation of CICR is important in suppression of arrhythmia.