Calcium and arrhythmia: from genes to teens to better drugs

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Calsequestrin is the most abundant Ca^{2+}-binding protein of the specialized endoplasmic reticulum found in muscle, the sarcoplasmic reticulum (SR). Calsequestrin binds Ca^{2+} with high capacity and low affinity and importantly contributes to the mobilization of Ca^{2+} during each contraction both in skeletal and cardiac muscle. Surprisingly, mutations in the gene encoding the cardiac isoform of calsequestrin (*CASQ2*) have been associated with an inherited form of ventricular arrhythmia triggered by emotional or physical stress termed Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). Despite normal cardiac contractility and normal resting ECG, CPVT patients present with a high risk of sudden death at a young age. CPVT is caused by mutations in genes involved in Ca^{2+} release from sarcoplasmic reticulum (SR) during excitation-contraction coupling (Chopra & Knollmann, 2011). The most common autosomal-dominant form of CPVT is associated with mutations in the *RYR2* gene encoding the ryanodine receptor (RyR2) SR Ca release channel. A rare form of autosomal-dominant CPVT is associated with mutations in *CALM1* encoding calmodulin. Autosomal-recessive CPVT has been associated with mutations in RyR2 binding proteins calsequestrin and triadin (Chopra & Knollmann, 2013). Experimental models of CPVT (*e.g.*, transgenic mice, induced pluripotent stem cells) have shed light on the pathophysiological mechanism underlying CPVT (Knollmann, 2013). Disease-causing CPVT mutations render RyR2 Ca release channels prone to spontaneous opening, resulting in spontaneous Ca release and propagated Ca waves that trigger membrane depolarizations, premature beats and polymorphic ventricular tachycardia during exercise or emotional stress. Furthermore, drugs that inhibit RyR2 channels in the open state and reduce Ca^{2+} wave frequency (Hilliard *et al.*, 2010) have been shown to prevent CPVT in mice and humans (Watanabe *et al.*, 2009). Since hyperactive RyR2 channels and spontaneous Ca^{2+} release can trigger arrhythmias in animal models of heart failure, RyR2 blockers could become a new approach for treating ventricular arrhythmias in the future.

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