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Titel des Beitrags:
Dantrolene rescues arrhythmogenic RYR2 defect in a patient-specific stem cell model of catecholaminergic polymorphic ventricular tachycardia.

Abstract:
Coordinated release of calcium (Ca(2+)) from the sarcoplasmic reticulum (SR) through cardiac ryanodine receptor (RYR2) channels is essential for cardiomyocyte function. In catecholaminergic polymorphic ventricular tachycardia (CPVT), an inherited disease characterized by stress-induced ventricular arrhythmias in young patients with structurally normal hearts, autosomal dominant mutations in RYR2 or recessive mutations in calsequestrin lead to aberrant diastolic Ca(2+) release from the SR causing arrhythmogenic delayed after depolarizations (DADs). Here, we report the generation of induced pluripotent stem cells (iPSCs) from a CPVT patient carrying a novel RYR2 S406L mutation. In patient iPSC-derived cardiomyocytes, catecholaminergic stress led to elevated diastolic Ca(2+) concentrations, a reduced SR Ca(2+) content and an increased susceptibility to DADs and arrhythmia as compared to control myocytes. This was due to increased frequency and duration of elementary Ca(2+) release events (Ca(2+) sparks). Dantrolene, a drug effective on malignant hyperthermia, restored normal Ca(2+) spark properties and rescued the arrhythmogenic phenotype. This suggests defective inter-domain
interactions within the RYR2 channel as the pathomechanism of the S406L mutation. Our work provides a new in vitro model to study the pathogenesis of human cardiac arrhythmias and develop novel therapies for CPVT.