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Dantrolene reduces CaMKII-mediated arrhythmogenesis

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Rationale: In atrial and ventricular rhythm disorders, an increased diastolic sarcoplasmatic reticulum (SR) calcium leak can induce a depolarizing transient inward current, serving as a trigger for cellular arrhythmias. Dantrolene has been shown to also stabilize the cardiac ryanodine receptor. However, the detailed mechanism of the mode of action remains unknown. This study aims to investigate the effects of dantrolene on calcium/calmodulin-dependent kinase II (CaMKII) mediated arrhythmogenesis.

Methods and results: Right atrial cardiomyocytes (CM) were isolated from patients with atrial fibrillation. To investigate SR Ca2+ leak, measurements of diastolic SR Ca2+ sparks were performed by confocal microscopy using Fluo-4 AM. Dantrolene (10 μmol/l) potently reduced Ca2+-spark-frequency (CaSpF) by 90±26% (p<0.05, n=21 cells dantrolene vs. 19 cells control) leading to a reduction of the calculated diastolic SR-Ca2+-leak by 91±31% (p<0.05, n=21 vs. 19). Interestingly, CaMKII-inhibition using Autocamtide-2-Related Inhibitory Peptide (AIP) did not further reduced SR Ca2+ leak compared to dantrolene alone in human cardiomyocytes. This observation may suggest (secondary) inhibitory effects of dantrolene on CaMKII. To elucidate the role of CaMKII in dantrolene-mediated antiarrhythmic effects, we investigated atrial CM from mice overexpressing CaMKII (TG) and respective wildtype controls (WT). CaSpF and SR Ca2+ leak were reduced by dantrolene in both TG and WT mice (p<0.005, TG: dantrolene vs. vehicle n=132 vs 127 cells (9 mice); WT: dantrolene vs. vehicle n=61 vs 61 cells (5 mice)). However, proarrhythmic Ca2+ waves were only significantly reduced by dantrolene in TG mice (p<0.05, TG: dantrolene vs. vehicle 10.8% vs. 26.2%, n=154 vs 164 cells).

Correspondingly, the incidence of delayed afterdepolarizations (DADs) in TG cells was significantly diminished by dantrolene (p<0.05, TG: dantrolene vs. vehicle 1/14 vs. 9/15 cells, n=5 mice). In contrast, DADs were not reduced by dantrolene in WT cells without increased CaMKII activity (p=n.s., WT: dantrolene vs vehicle 3/16 vs 2/13 cells, n=5 mice). In preliminary in vivo experiments, intraperitoneal injection of 40 mg/kg body weight dantrolene reduced the inducibility of arrhythmias by ventricular burst stimulation in CaMKII TG mice compared to vehicle (dantrolene 0/2 mice vs. vehicle 2/2 mice, p<0.05 Chi-Square).

Conclusion: Dantrolene beneficially altered Ca2+ homeostasis in human AF CM and murine CM. Dantrolene seems to exert its antiarrhythmic potential in a CaMKII-dependent manner. Thus, dantrolene as an already clinically approved compound might be a potential antiarrhythmic drug that merits clinical investigation.