Aberrant function of calcium releases channels underlying sudden cardiac death probed with RyR domain peptides

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Sudden cardiac death (SCD) is a significant health issue because of its unpredictability and devastating outcome. Recently, two distinct types of SCD have been linked to eleven mutations in the cardiac ryanodine receptor (RyR_2), the major calcium release channel in the sarcoplasmic reticulum (SR). Seven of these mutations are clustered in two regions located at aa2200-2500 (central domain) and aa4100-4650 (c-terminal) (1). These regions coincide with regions the skeletal muscle isoform (RyR_1) that give rise to malignant hyperthermia. This has lead to the hypothesis that interactions between these central and c-terminal domains are important for normal channel function.

Recently, synthetic peptides corresponding to sections of the RyR were used to identify the regions of the RyR_2 that were critical for channel function. One such peptide, designated DPc10, corresponds to the Gly^{2460}-Pro^{2495} in RyR_2. The present study investigates if DPc10 can disrupt inter-domain interactions by competing with corresponding regions of the RyR and if this can mimic the effects of mutations associated with SCD on RyR_2 function in lipid bilayers.

DPc10 (100 μM) reversibly increased the open probability of RyR_2 in the presence of cytoplasmic $[Ca^{2+}]$ <1 μM while at higher $[Ca^{2+}]$ DPc10 had relatively little effect. The DPc10 activation we see is similar to that seen in RyR_2 containing mutations in the central region of the RyR_2 (2). Interestingly, by incorporating a mutation in DPc10 corresponding to Arg2475Ser (DPc10mut) abolished the effects of DPc10 across all calcium concentrations. This indicates that the mutation disrupts binding of DPc10 to the RyR and that the Arg 2475 Ser mutation in the RyR can disrupt binding between Gly^{2460}-Pro^{2495} and its corresponding domain.

(1) Yamamoto T and Ikemoto N, Biochem Biophys Res Commun. 2002;291:1102-1108.
(2) Lehnart et al. Circulation. 2004;109:r113-r119.