Microdomain-specific beta-adrenergic regulation of calcium signaling in tachycardia-induced atrial fibrillation

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Authors: Cuypers, Anne

Advisors: ANTOONS, Gudrun

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Abstract: To our knowledge, no studies have been performed to investigate microdomain-specific protein kinase A (PKA)-dependent-phosphorylation of ryanodine receptors (RyR) during β-adrenergic modulation in atrial fibrillation (AF). Therefore, atrial myocytes from sham-operated- (SHAM) and rapid atrial paced (RAP; 5 days at 10 Hz) rabbits were stimulated under baseline or after β-adrenergic stimulation (Isoproterenol, 300 nM). Ca2+ transients were measured confocally during field stimulation (1 Hz, 37 °C). PKA-dependent RyR phosphorylation was analyzed by immunostaining and assigned to the nearest membrane. Confocal images were analyzed using ImageJ. Statistical significance (p<0.05) was evaluated with Student's t-test, Mann-Whitney U test, or ANOVA. At global level in atrial RAP cells, amplitude of Ca2+ transients and RyR phosphorylation were significantly reduced at baseline, but normalized after β-adrenergic stimulation. At microdomain level in atrial RAP cells, β-adrenergic rescue of RyR phosphorylation involved equal recruitment of RyR at uncoupled, subsarcolemmal and axial regions. In atrial myocytes, level of PKA-dependent RyR phosphorylation depends on the subcellular location. Atrial remodeling due to rapid pacing causes RyR hypophosphorylation that can be reversed by β-adrenergic stimulation. This mechanism could, at least partly, contribute to the β-adrenergic rescue of Ca2+ transients in AF improving contractility, but could adversely increase the likelihood of arrhythmias.

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