Function of adrenergic-stimulated cardiac RyRs

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In cardiomyocytes, calcium is released from SR intracellular stores through ryanodine receptors (RyR). RyRs are regulated by Ca^{2+} in both the cytoplasm and SR lumen and their proper regulation plays an important role in cardiac output. Additionally, cardiac output is increased by stimulation of β-adrenergic receptors (β-AR) by adrenaline and noradrenaline. β-ARs couple to Gsα-protein, leading to phosphorylation of numerous targets including the RyRs. There are conflicting reports about how, and where, RyRs are phosphorylated *in situ* and there is no consensus on the effects of phosphorylation on RyR activity. Our objective is to understand how adrenergic-stimulation of cardiomyocytes influences the function of RyRs. Hearts were rapidly removed from adult male Sprague-Dawley rats and perfused with Krebs solution in a Langendorff apparatus (5 min). Hearts were then perfused (5 min) with Krebs solution containing 1 μM isoproterenol (β1-adrenergic agonist) or with Krebs alone (control). Hearts were rapidly frozen in liquid N2 and stored at -80°C. RyRs were isolated from these hearts and incorporated into artificial planar lipid bilayers and their activity was measured using single channel recording. RyRs (n=10) from control hearts were activated by both cytoplasmic and luminal Ca^{2+}. The mean activity of RyRs from isoproterenol-stimulated hearts was 10-fold higher than control RyRs at diastolic [Ca^{2+}] (100 nM) but was not significantly different at systolic [Ca^{2+}] (>1 μM, n=19). Moreover, RyRs from stimulated hearts showed a bimodal distribution in activity with one population (12 out of 19) similar to RyRs from control hearts and another, excited population (7 out of 19) with reduced channel mean close times. Hence, adrenergic-stimulation changes the gating of RyRs *in situ* by increasing channel opening rates.