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Abstract: 181P

IP_3R activity increases propensity of RyR-mediated Ca^{2+} sparks by elevating dyadic [Ca^{2+}]

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The heart's pumping action is governed by the concerted contraction and relaxation of individual cardiomyocytes through the excitation-contraction coupling (ECC) process. During ECC, the cell wide Ca^{2+} release responsible for engaging the cardiomyocyte's contractile machinery is composed of elementary Ca^{2+} release units termed Ca^{2+} sparks, which materialize due to the activation of ryanodine receptors (RyRs) primarily located at 10 – 15 nm wide intracellular microdomains called dyads. While RyRs are the primary Ca^{2+} channels responsible for generating the cell-wide Ca^{2+} transients during ECC, Ca^{2+} release via inositol 1,4,5-trisphosphate (IP_3) receptors (IP_3Rs) are also reported in cardiomyocytes and are demonstrated to elicit ECC-modulating effects. It is proposed that IP_3Rs' ability to modulate ECC is granted by their colocalization with RyRs at functionally relevant sites in the cardiomyocyte, of which includes dyads. Several studies have indeed reported an increase in Ca^{2+} spark frequency under IP_3R stimulation (1–3). However, the mechanism underlying this observation is not fully resolved.

In this study, we aim to uncover the mechanism by which dyad-localized IP_3Rs influence Ca^{2+} sparks and reveal their effect on local Ca^{2+} handling. To this end, we utilized mathematical models of RyRs and IP_3Rs and developed a spatial computational model of the dyad to simulate an environment where clusters of both Ca^{2+} channels are colocalized. Consistent with published experimental data, our biophysics-based simulations predict that this hetero channel crosstalk increases the propensity for RyR-mediated Ca^{2+} spark formation. The stochasticity of IP_3R gating is a key feature to eliciting this outcome. In terms of local Ca^{2+} handling, dyadic IP_3R activity lowers the Ca^{2+} available in the junctional sarcoplasmic reticulum (JSR) for release, thus resulting in Ca^{2+} sparks with lower amplitudes but similar durations. Overall, our results support the hypothesis that IP_3Rs facilitate Ca^{2+} spark formation by raising dyadic Ca^{2+} concentration ([Ca^{2+}]), thereby priming RyRs for future activation.

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