MAR05-2004-001586

Abstract for an Invited Paper
for the MAR05 Meeting of
the American Physical Society

Excitation-contraction coupling gain and cooperativity of the cardiac ryanodine receptor: a modeling approach

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During calcium-induced-calcium-release, the ryanodine receptor opens and releases large amounts of calcium from the sarcoplasmic reticulum into the cytoplasm of the myocyte. Recent experiments have suggested that cooperativity between the four monomers comprising the ryanodine receptor plays an important role in the dynamics of the overall receptor. Furthermore, this cooperativity can be affected by the binding of FK506 binding protein and hence modulated by adrenergic stimulation through the phosphorylating action of PKA. This has important implications for heart failure, where it has been hypothesized that ryanodine receptor hyperphosphorylation, resulting in a loss of cooperativity, can lead to a persistent leak and a reduced sarcoplasmic reticulum content. Here, we report on a theoretical model that examines the cooperativity via the assumption of an allosteric interaction between the four subunits. We find that the level of cooperativity, regulated by the binding of FK506 binding protein, can have a dramatic effect on the excitation-contraction coupling gain and that this gain exhibits a clear maximum. These findings offer a simple explanation of heretofore conflicting data from different species and allows for an evaluation of the aforementioned heart failure scenario.