Gating mechanisms of the sarcoplasmic reticulum calcium channel

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ABSTRACT

We have developed a model of the ryanodine receptor – the calcium channel of the sarcoplasmic reticulum. The model accurately describes available experimental data on the channel activity at various concentrations of calcium ions, caffeine and quercetin. The proposed mechanism is the allosteric regulation of calcium ion affinity by both caffeine and quercetin, and the existence of two independent gates controlled by ligand binding to the receptor. By fitting the data we are able to derive binding affinities and Hill coefficients of the ligands, and explain why quercetin is an activating agent stronger than caffeine, or how caffeine and quercetin can activate the channel at very low Ca^{2+} concentration ($\sim 10^{-11}$ M). We predict that the activation regime at saturating caffeine or quercetin should present four distinct regions at increasing Ca^{2+}, corresponding to the successive increase in the open probability due to each monomer of the receptor. Another interesting prediction is the enlargement of the activity domain toward higher Ca^{2+} concentrations in the presence of caffeine or quercetin.