Mapping Co-regulatory Interactions among Ligand Binding sites in RyR1

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Abstract

Ryanodine receptor 1 (RyR1) is an intracellular calcium ion (Ca2+) release channel required for skeletal muscle contraction. Although cryo-electron microscopy identified binding sites of three coactivators Ca2+, ATP and caffeine (CFF), the mechanism of co-regulation and synergy of these activators is unknown. Here, we report allosteric connections among the three ligand binding sites and pore region in (i) Ca2+ bound-closed, (ii) ATP/CFF bound- closed, (iii) Ca2+/ATP/CFF bound-closed, and (iv) Ca2+/ATP/CFF bound-open RyR1 states. We identified two dominant interactions that mediate interactions between the Ca2+ binding site and pore region in Ca2+ bound-closed state, which partially overlapped with the pore communications in ATP/CFF bound-closed RyR1 state. In Ca2+/ATP/CFF bound-closed and -open RyR1 states, co-regulatory interactions were analogous to communications in the Ca2+ bound-closed and ATP/CFF bound- closed states. Both ATP- and CFF- binding sites mediate communication between the Ca2+ binding site and the pore region in Ca2+/ATP/CFF bound - open RyR1 structure. We conclude that Ca2+, ATP, and CFF propagate their effects to the pore region through a network of overlapping interactions that mediate allosteric control and molecular synergy in channel regulation.

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