A Drug And ATP Binding Site In Type 1 Ryanodine Receptor

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The ryanodine receptor (RyR)/calcium release channel on the sarcoplasmic reticulum (SR) is required for excitation-contraction coupling in skeletal and cardiac muscle. Inherited mutations and stress-induced post-translational modifications result in a SR Ca2+ leak that causes skeletal myopathies, heart failure, and exercise-induced sudden death. A class of therapeutics known as Rycals prevent the RyR-mediated leak, are effective in preventing disease progression and restoring function in animal models, and are in clinical trials for patients with muscle and heart disorders. Using cryogenic-electron microscopy we present a model of RyR1 with a 2.45 Å resolution prior to local refinement revealing a binding site in the RY1&2 domain (3.10 Å local resolution) where the Rycal ARM210 binds cooperatively with ATP and stabilizes the closed state of RyR1.