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Both Quantitative and Qualitative Alterations of Ca^{2+} Release Channel in Heart are Induced by Chronic Treatment of an Immunosuppressant, Cyclosporin A

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Chronic treatment with cyclosporin A (CsA) were shown to induce reversible alterations of contractile properties in rat heart. To define the molecular mechanisms underlying the physiological alterations, the Ca^{2+} release channel (CRC) and Ca^{2+}-ATPase in rat sarcoplasmic reticulum (SR) were examined. Ryanodine binding to whole homogenates of rat hearts shows time- and dose-dependent alterations in CRC properties by CsA: upon 3 weeks treatment, maximal ryanodine binding (B_{max}) decreased, the dissociation constant of ryanodine (K_d) increased, caffeine sensitivity of CRC increased, ruthenium red sensitivity of CRC decreased, slope conductance of CRC decreased, and mean open probability (P_o) of CRC increased significantly. However, the Ca^{2+} sensitivity of ryanodine binding was not affected by CsA. On the other hand, B_{max} and K_d of ryanodine binding in rat skeletal muscles were not changed. Ryanodine-sensitive oxalate-supported Ca^{2+} uptake in whole homogenates was significantly lower in CsA-treated rat hearts, while total Ca^{2+} uptake in the presence of 500 μM ryanodine was not changed. These heart muscle-specific alterations of CRC could be responsible for the previously reported contractile changes of CsA-treated rat hearts.