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Characterization of Single Channel Properties of Cardiac Ca^{2+} Release Channel in Rats Treated with the Immunosuppressant Drug, Cyclosporin A

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Cyclosporin A (CsA) is widely used to suppress rejection in recipients of solid organ or bone marrow transplants. A variety of toxic side effects of this agent such as cardiotoxicity have been reported. However the underlying molecular mechanisms for the cardiotoxicity are not well resolved. The aim of this study was to define the alterations of the Ca^{2+} release channels in sarcoplasmic reticulum (SR) of rat hearts at the single channel level using planar lipid bilayer method. The animals for the experimental group were treated with CsA dissolved in cremophor at the dose of 15mg/kg body wt./day for 21 days by subcutaneous injection. The animals injected with cremophor served for control. The SR from the rat hearts were isolated by sucrose density gradient centrifugation and subjected to the single channel studies. The following changes were found in the Ca^{2+} release channel from the CsA-treated animals: in the presence of 100 μM $CaCl_2$ and 10 mM caffeine, 1) the slope conductance decreased, 2) the open probability increased due to a longer mean open, 3) ryanodine-induced half-conductance state of the channel was incomplete. On the other hand, 10 μM ruthenium red completely blocked Ca^{2+} release channel in both control and CsA groups. These findings suggest that the chronic treatment of cyclosporin A induces qualitative changes of the Ca^{2+} release channel at single channel level.