Refractoriness of SR-Calcium Release after betaadrenergic Stimulation in Cardiac Myocytes

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Some mechanisms of the Ca^{2+}-induced Ca^{2+} release (CICR) are still a matter of debate, such as regulation of CICR. We have observed that in cardiac myocytes coherent activation of SR Ca^{2+} release induced refractoriness of CICR. It has been suggested that SR Ca^{2+} depletion and refilling may underlie refractoriness. Here we examined whether β-adrenergic stimulation could affect CICR. We used UV-laser flash photolysis of caged Ca^{2+} in combination with the whole-cell patch clamp technique to activate Na^{+}-Ca^{2+} exchange currents in guinea pig ventricular myocytes. Pairs of UV-flashes were applied at various intervals to follow the time-course of recovery from refractoriness. β-adrenoreceptor stimulation affected SR Ca^{2+} content in two different ways. (1) Whereas the SR Ca^{2+} content was decreased when isoproterenol (Iso) treatment began after SR reloading, it was elevated if SR reloading was performed during Iso superfusion. (2) β-adrenergic stimulation (after SR reloading) resulted in a faster recovery of CICR from refractoriness. SR Ca^{2+} content and RyR phospho-rylation both could lead to changes in Ca^{2+} sensitivity of CICR. Application of 1µM Iso reduced the refractoriness, such that complete recovery of Ca^{2+} release could be observed earlier. We conclude that β-adrenergic stimulation may modulate global CICR refractoriness. This might result from acceleration of SR Ca^{2+} refilling or from a change of the Ca^{2+} sensitivity and/or gating kinetics of the RyRs.