Hypertrophic Cardiomyopathy Mutants of Troponin C Alter Its Affinity for the Thin Filament

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Troponin is a regulatory protein of vertebrate striated muscle contraction. Its three subunits are TnT, which binds to tropomyosin; TnI, the inhibitory component; and TnC, the Ca^{++}-binding subunit. In cardiac muscle, mutations of the troponin gene can lead to cardiomyopathy phenotypes. Recently, four new mutations that cause hypertrophic cardiomyopathy were discovered in cardiac TnC: A8V, in the N-terminus; C84Y, in the central helix; and E134D and D145E, in the C-terminal. It has been shown elsewhere that three of these mutants increase the N-terminus Ca^{++} affinity. Considering that the affinity for the thin filament depends on the C-terminus, the objective of the present study was to investigate the influence of these mutations on the interaction between TnC and the thin filament in striated and cardiac muscle skinned fibers. TnC dissociation experiments were performed in relaxed fibers (in mM: 0.001 Mg^{++}, 20 imidazole propionate, 10 K_2EDTA, 3.3 MgATP, pH 7.0, 15°C) to evaluate TnC-thin filament affinity. The native TnC was replaced with a mutant, and during 5-60 min of TnC loss the residual tension was measured periodically at pCa 4.4. The results indicate a lower TnC-thin filament affinity (faster TnC loss) for the C-terminus mutants in striated muscle ($t_{½}$ (min) 8.7, control; 6.9, A8V; 15, C84Y; 5.4, E134D and 2.8, D145E). In cardiac muscle the C-terminus mutants dissociated more slowly than the control ($t_{½}$ (min) 12.7, control; 8, A8V; 19.5, E134D and 41.2, D145E). Thus the C-domain mutations alter TnC-thin filament affinity, but have opposite effects in striated and cardiac thin filaments.

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