Analysis of CICR control mechanism using molecular dynamics simulation and malignant hyperthermia model mouse

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Mutations in type 1 ryanodine receptor (*RyR1*) gene cause severe muscle diseases, such as malignant hyperthermia (MH), which is a disorder of Ca^{2+}-induced Ca^{2+} release via RyR1 in the skeletal muscle. We combined functional studies and molecular dynamics (MD) simulations of RyR1 bearing disease-associated mutations at the N-terminal region. When expressed in HEK293 cells, the mutant RyR1 caused abnormalities in Ca^{2+} homeostasis. MD simulation of the mutant RyR1 revealed that alterations of hydrogen bonds/salt bridges between N-terminal domains (NTD), consisting of A, B and C domains, strongly correlate with the channel function of RyR1. Next, we tested therapeutic effects of RyR1 inhibitor on MH model mice carrying mutation in the *RYR1* gene. RyR1 inhibitor suppressed caffeine-induced contraction in skeletal muscle from heterozygous MH mice. The heterozygous mice died with an increased body temperature when they were anesthetized by isoflurane. Pre-administration of RyR1 inhibitor completely prevented rise in the body temperature and death. In addition, RyR1 inhibitor rescued the mice after they developed MH episodes. These results suggest that RyR1 mutant mice will be promising model mice for MH pathogenesis and screening of new drugs.