Excitability and Ca^{2+} handling defects in skeletal muscle fibers from a zebrafish model of Bethlem myopathy

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Bethlem myopathy (BM) is a muscle disease characterized by joint contractures and muscle weakness worsening with age. BM results from mutations in genes encoding one of the three α chains of collagen VI (COLVI), a component of the skeletal muscle extracellular matrix produced by interstitial fibroblasts. A still unresolved issue in BM is how alteration in COLVI present outside muscle fibers induces dysfunction within muscle fibers. In the present study, a zebrafish line (*col6a1*$^{\Delta ex14}$) harboring an exon-skipping mutation that is the most frequently found in BM has been used to determine whether muscle dysfunction caused by BM mutation results from alteration in muscle excitation and/or intracellular Ca^{2+} homeostasis. Current- and voltage-clamp experiments and Ca^{2+} measurements were performed in isolated fast trunk muscle fibers from 1-year old mutant fish, which have much more severe disease phenotype than larvae or juvenile fish. Muscle action potentials were found to be unchanged in mutant fish. The voltage-dependence of charge movements produced by depolarization-induced activation of dihydropyridine receptors (DHPRs) that control sarcoplasmic reticulum Ca^{2+} release was found to be significantly shifted toward negative potentials in mutant fish. Concomitantly, the voltage-dependence of depolarization-evoked intracellular Ca^{2+} transients measured with the Ca^{2+} indicator indo-1 were also shifted toward negative voltages and Ca^{2+} transients were more sustained and inactivated for more positive depolarizations in mutant fish. These data suggest that the voltage control of activation and inactivation exerted by the DHPR on sarcoplasmic reticulum Ca^{2+} release is altered in muscles from zebrafish carrying the BM mutation.