Ca2+ handling abnormalities in early-onset muscle diseases: Novel concepts and perspectives.

Treves S1, Jungbluth H2, Voermans N3, Muntoni F4, Zorzato F5.

Abstract

The physiological process by which Ca\textsuperscript{2+} is released from the sarcoplasmic reticulum is called excitation-contraction coupling; it is initiated by an action potential which travels deep into the muscle fiber where it is sensed by the dihydropyridine receptor, a voltage sensing L-type Ca\textsuperscript{2+} channel localized on the transverse tubules. Voltage-induced conformational changes in the dihydropyridine receptor activate the ryanodine receptor Ca\textsuperscript{2+} release channel of the sarcoplasmic reticulum. The released Ca\textsuperscript{2+} binds to troponin C, enabling contractile thick-thin filament interactions. The Ca\textsuperscript{2+} is subsequently transported back into the sarcoplasmic reticulum by specialized Ca\textsuperscript{2+} pumps (SERCA), preparing the muscle for a new cycle of contraction. Although other proteins are involved in excitation-contraction coupling, the mechanism described above emphasizes the unique role played by the two Ca\textsuperscript{2+} channels (the dihydropyridine receptor and the ryanodine receptor), the SERCA Ca\textsuperscript{2+} pumps and the exquisite spatial organization of the membrane compartments endowed with the proteins responsible for this mechanism to function rapidly and efficiently. Research over the past two decades has uncovered the fine details of excitation-contraction coupling under normal conditions while advances in genomics have helped to identify mutations in novel genes in patients with neuromuscular disorders. While it is now clear that many patients with congenital muscle diseases carry mutations in genes encoding proteins directly involved in Ca\textsuperscript{2+} homeostasis, it has become apparent that mutations are also present in genes encoding for proteins not thought to be directly involved in Ca\textsuperscript{2+} regulation. Ongoing research in the field now focuses on understanding the functional effect of individual mutations, as well as understanding the role of proteins not specifically located in the sarcoplasmic reticulum which nevertheless are involved in Ca\textsuperscript{2+} regulation or excitation-contraction coupling. The principal challenge for the future is the identification of drug targets that can be pharmacologically manipulated by small molecules, with the ultimate aim to improve muscle function and quality of life of patients with congenital muscle disorders. The aim of this review is to give an overview of the
most recent findings concerning Ca\textsuperscript{2+} dysregulation and its impact on muscle function in patients with congenital muscle disorders due to mutations in proteins involved in excitation-contraction coupling and more broadly on Ca\textsuperscript{2+} homeostasis.

**KEYWORDS:** Ca(2+) homeostasis; Congenital myopathies; Dihydropyridine receptor; Excitation-contraction coupling; Mutations; Ryanodine receptor; SERCA; Sarcoplasmic reticulum

PMID: 27427513  DOI: 10.1016/j.semcdb.2016.07.017

[Indexing for MEDLINE]