Impaired neuromuscular transmission and skeletal muscle fiber necrosis in mice lacking Na/Ca exchanger 3.


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Abstract

We produced and analyzed mice deficient for Na/Ca exchanger 3 (NCX3), a protein that mediates cellular Ca(2+) efflux (forward mode) or Ca(2+) influx (reverse mode) and thus controls intracellular Ca(2+) concentration. NCX3-deficient mice (Ncx3(-/-)) present a skeletal muscle fiber necrosis and a defective neuromuscular transmission, reflecting the absence of NCX3 in the sarcolemma of the muscle fibers and at the neuromuscular junction. The defective neuromuscular transmission is characterized by the presence of electromyographic abnormalities, including low compound muscle action potential amplitude, a decremental response at low-frequency nerve stimulation, an incremental response, and a prominent postexercise facilitation at high-frequency nerve stimulation, as well as neuromuscular blocks. The analysis of quantal transmitter release in Ncx3(-/-) neuromuscular junctions revealed an important facilitation superimposed on the depression of synaptic responses and an elevated delayed release during high-frequency nerve stimulation. It is suggested that Ca(2+) entering nerve terminals is cleared relatively slowly in the absence of NCX3, thereby enhancing residual Ca(2+) and evoked and delayed quantal transmitter release during repetitive nerve stimulation. Our findings indicate that NCX3 plays an important role in vivo in the control of Ca(2+) concentrations in the skeletal muscle fibers and at the neuromuscular junction.