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Modeling the slow cytotoxic swelling of dystrophic muscle fibers

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In Duchenne muscular dystrophy (MD) patients, muscle fiber Na+-loading is linked to cytotoxic swelling. Quiescent fibers move away from their resting membrane potential Vrest (and towards Donnan equilibrium) due to concurrently open Na+ and Cl- conductances that together underlie the swelling and depolarization. Since a chloride conductance (ClC-1) underlies healthy Vrest in fibers, whatever underlies the Na+-loading is the pathologic conductance. Indeed, increased Na/K pump activity counteracts swelling and promotes repolarization (see review by Morris (Curr Topics Memb 81, 2018)). The classic animal model for Duchenne MD is the dystrophin-less mouse, mdx. Wild-type muscle fibers are better able to resist mechanically-induced (pipette aspiration) sarcolemmal blebbing than mdx fibers and they more effectively use caveolar tension buffering to maintain sarcolemmal integrity. In 3-day survival experiments, isolated fiber survival is markedly worse in mdx than in wild-type. The Na+ channel blocker Tetrodotoxin provides full protection for mdx fibers, indicating that the mdx fibers have "leaky"Nav1.4 channels. We postulate that it is specifically the Nav1.4 channels resident in bleb-damaged areas of dystrophic sarcolemma that would exhibit left-shifted operation. The result –an increased gNa(V) window conductance at abnormally hyperpolarized voltages – would continually stress ion homeostatic processes, making it likely that cytotoxic swelling would eventually become evident. We built an MD muscle cell model including ion concentrations, conductances, pumps, volume, membrane potential and tensions. Damage is represented by a coupled left shift (CLS) of the activation and inactivation kinetics of a fraction of the Nav channels. The model predicts cytotoxic swelling with anoxia (no pump activity). It shows the tolerance of the muscle cell to damage, with no swelling until a critical state. It explains also how increased pump activity can keep the swelling under control.

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