Skeletal muscle function: the role of ionic changes in fatigue, damage and disease

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Repeated activity of skeletal muscle changes its properties in a variety of ways; muscles become weaker with intense use (fatigue), may feel sore and tender after excessive use, and can degenerate in many disease conditions. Early ionic changes are critical to the development of each of these conditions.

Central to this experimental approach has been the development of the single fibre preparation of mouse muscle. Individual cells can be dissected with intact tendons and stimulated to produce force. Fluorescent indicators can be micro-injected into the fibres and intracellular Ca^{2+}, Na^{+}, pH, Mg^{2+}, ATP etc can all be measured from one cell whilst simultaneously monitoring the mechanical performance. Other substances can be injected into the cells (proteins, peptides, caged compounds, plasmids etc) and after activity the cell can be prepared for immunohistochemistry, light microscopy, electron microscopy etc.

In 1988 when we started this work, the dominant theory was that intracellular acidosis caused muscle fatigue. In contrast we found that single fibres could fatigue with little or no pH change (Westerblad & Allen, 1992) but failure of calcium release was found to be a major cause of fatigue (Westerblad & Allen, 1991). Currently we propose that precipitation of calcium and phosphate in the sarcoplasmic reticulum contributes to the failure of calcium release (Allen & Westerblad, 2001).

Muscles can be used to shorten and produce force or they can be used to deaccelerate loads (eccentric contractions). A day after intense eccentric exercise muscles are weak, sore and tender and this damage can take a week to recover. In this condition sarcomeres are disorganised and there are increases in resting Ca^{2+} and Na^{+} (Balnave & Allen, 1995; Yeung *et al.*, 2003). Recently we discovered that the elevation of Na^{+} occurs through a stretch-activated channel which can be blocked by either gadolinium or streptomycin. Preventing the rise of $[Na^{+}]_i$ with gadolinium also prevents part of the muscle weakness after eccentric contractions (Yeung *et al.*, 2003).

Duchenne muscular dystrophy is a lethal degenerative disease of muscles in which the protein dystrophin is absent. Dystrophic muscles are more susceptible to stretch-induced muscle damage and the stretch-activated channel seems to be one pathway for the increases in intracellular Ca^{2+} and Na^{+} which are a feature of this disease. We have recently shown that blockers of the stretch-activated channel can minimize some of the short-term damage in muscles from the *mdx* mouse, which also lacks dystrophin (Yeung *et al*., submitted). Currently we are testing whether blockers of the stretch-activated channels given systemically to *mdx* mouse can protect against some features of this disease.

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