Mitochondrial myopathies

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Mitochondrial myopathies are caused by genetic mutations that directly influence mitochondrial function. We have studied mechanisms underlying the impaired muscle function in several mouse models of mitochondrial myopathy. Experiments were mainly performed on single muscle fibres where force and $[Ca^{2+}]_i$ were simultaneously measured. Furthermore, mitochondrial matrix $[Ca^{2+}]$ ($[Ca^{2+}]_{mit}$) and reactive oxygen species (ROS) were measured as these parameters have been implicated in the development of mitochondrial disorders. Protein changes that might cause the observed functional changes were assessed. Experiments were performed on muscles that were isolated after the mouse had been killed by rapid neck disarticulation. The results show that muscle weakness due to a decreased sarcoplasmic reticulum (SR) Ca^{2+} release is a key defect in mitochondrial myopathies (Aydin *et al.*, 2009). The decreased Ca^{2+} release can be explained by a reduced SR Ca^{2+} loading capacity. Increased $[Ca^{2+}]_{mit}$ during repeated contractions appears to be an important cause of the muscle weakness, and muscle function is improved when the mitochondrial Ca^{2+} uptake is inhibited. We saw no signs of increased ROS production in mitochondrial myopathy muscles.

In conclusion, the observed changes in Ca^{2+} handling can be seen as adaptive responses to progressively failing mitochondrial ATP production. A reduced SR Ca^{2+} release will effectively decrease ATP expenditure, and increased $[Ca^{2+}]_{mit}$ can stimulate mitochondrial respiration. However, reduced SR $[Ca^{2+}]$ causes muscle weakness and increased $[Ca^{2+}]_{mit}$ may be harmful in the long run by inducing cell damage.

Aydin J, Andersson DC, Hänninen SL, Wredenberg A, Tavi P, Park CB, Larsson NG, Bruton JD & Westerblad H. (2009). Increased mitochondrial Ca^{2+} and decreased sarcoplasmic reticulum Ca^{2+} in mitochondrial myopathy. *Human Molecular Genetics* **18,** 278-288.