The Regulation of Mitophagy in Response to Hindlimb Denervation

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During chronic muscle disuse, fibre atrophy occurs concomitantly with reductions in mitochondrial content and function, due to depressed mitochondrial biogenesis and elevations in degradation. The regulation of mitochondrial biogenesis has been studied extensively. However, the processes that underlie the degradation of mitochondria have yet to be fully elucidated. The breakdown of the organelle is due to a selective form of autophagy, termed mitophagy. When a mitochondrion becomes dysfunctional it dissociates from the mitochondrial network and is subsequently degraded by lysosomes. The objective of this work is to better understand the process of mitophagy in the context of muscle disuse. Accordingly, we employed a hindlimb denervation protocol in which we unilaterally sectioned the peroneal nerve of one hindlimb, using the contralateral limb as a control in Sprague-Dawley rats. Protein measurements of autophagy and mitochondrial content markers were made at 1, 3 and 7 days post-denervation. We observed significant 25-30% (p<0.05) reductions in tibialis anterior (TA) and extensor digitorum longus (EDL) muscle mass by 7 days post-denervation. Significant elevations in the autophagy proteins were measured 7 days post denervation, while mitochondrial protein and enzyme activity were reduced by 25%-40%. To investigate the early changes in mitophagy flux that may explain the alterations in mitochondrial content and function, a subgroup of animals was treated with colchicine (4mg/kg/day) for 2 days to inhibit mitophagic breakdown in response to 1 and 3 days of denervation. Mitophagy flux was increased in by denervation, coinciding with declines in mitochondrial function, suggesting that mitochondrial degradation is not sufficient to eliminate all of the dysfunctional organelles. Furthermore, the immediate elevations in mitophagy flux occurred prior to the upregulation of autophagy marker, suggesting that the intrinsic activity of the autophagosomal breakdown pathway is sufficient in the early time course, but is subsequently upregulated to meet the demands of prolonged denervation.