Calpains and skeletal muscle function

R.M. Murphy and G.D. Lamb, Department of Zoology, La Trobe University, Melbourne, VIC 3086, Australia.

Skeletal muscle fibres contain ubiquitous (μ-calpain and m-calpain) and muscle-specific (calpain-3), Ca^{2+}-dependent proteases. Their physiological roles are not well understood, although ubiquitous calpains have been associated with apoptosis and myogenesis and calpain-3 has been suggested to be involved in sarcomeric remodeling. A defect in the expression of calpain-3 results in limb-girdle muscular dystrophy type 2A. Contrary to the dogma published from biochemical experiments that described calpain-3 as undergoing spontaneous autolysis (and hence activation) (Sorimachi *et al.,* 2006), we have shown that this protease is stable unless exposed to [Ca^{2+}] above resting physiological levels (> 50 nM). Our work has characterized the Ca^{2+}- and time-dependencies of μ-calpain and calpain-3 in muscle homogenates, importantly with physiological ionic conditions preserved. During normal activity, skeletal muscle undergoes frequent episodes of high intracellular [Ca^{2+}] and to understand how calpains are regulated during such periods, we have investigated various properties (such as diffusibility, binding and autolysis) of μ-calpain and calpain-3 using mechanically-skinned single fibres (Murphy, Venburg & Lamb, 2006). In addition, we have seen that overall the calpains were found not to be activated immediately following sprint, endurance or eccentric exercise in healthy human subjects (Murphy, Snow & lamb, 2006; Murphy *et al.,* 2007). Notably, we found that a substantial proportion of calpain-3, but not μ-calpain, was activated 24 h after the eccentric exercise bout, which could possibly be explained by the small but sustained increase in intracellular [Ca^{2+}] that occurs following eccentric contractions (Lynch, Fary & Williams, 1997) being both high and long enough to result in calpain-3 activation.

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