Sensory pathways of muscle phenotypic plasticity: Calcium signalling through CaMKII

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Abstract

Skeletal muscle can adapt its structure to cope with the mechanical and metabolic stresses placed on it by various amounts and patterns of human movement. The release of calcium into the cytoplasm of muscle fibres is thought to have an important role in these adaptations, yet the calcium-dependent signalling pathways involved haven't been fully defined. Calcium/calmodulin-dependent protein kinase II (CaMKII) has been presumed to drive mitochondrial biogenesis in skeletal muscle, but this has not been investigated *in vivo*.The experiments in this thesis aimed to address how CaMKII is activated in response to electrical stimulation of skeletal muscle and how CaMKII affects the muscle phenotype. A rat model was used for two main reasons: 1) it allowed for imposing well-defined stimulation patterns onto phenotypically homogenous muscle fibre populations under controlled conditions *in situ*, and investigating the molecular response to these stimulation patterns, and 2) it allowed for manipulation of CaMKII signalling in muscle fibres *in vivo* through the use of electro-assisted somatic gene transfer.It was hypothesised that CaMKII would be activated in a muscle and recruitment pattern specific manner. Furthermore, it was hypothesised that CaMKII overexpression would increase the expression of mitochondrial markers. In chapter 2, the effect of recruitment frequency on CaMKII phosphorylation in slow-twitch *m. soleus* and fast-twitch *m. gastrocnemius medialis* is investigated. Furthermore, the time course of CaMKII phosphorylation after muscle stimulation is studied. Chapter 3 presents a study into the effects of *in vivo* CaMKII overexpression in *m. soleus* and *m. gastrocnemius* on mitochondrial gene expression and muscle contractile function. The effects of CaMKII overexpression on skeletal alpha-actin transcription are presented in chapter 4. In chapter 5, a mathematical model of CaMKII activation in sarcomeres is described, and used to investigate the effects of CaMKII overexpression on calcium handling and on contractile properties of a muscle fibre. It was concluded that CaMKII is activated by very brief stimulation in a recruitment frequency-independent manner, and that increased CaMKII protein levels increase SERCA expression, but not mitochondrial gene expression.