EC coupling in skeletal muscle: implications for fatigue

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Skeletal muscle fibres are activated by a sequence of events referred to as excitation-contraction (EC) coupling. The action potential (AP) passes along the sarcolemma and into the transverse tubular (T-) system where it activates voltage-sensor molecules (VS) that in turn open the Ca^{2+} release channels in the sarcoplasmic reticulum (SR). The Ca^{2+} released into the cytoplasm activates the contractile apparatus, producing force. When skeletal muscles are stimulated repeatedly, they fatigue, that is there is a decrease in force and power output. There can be various causes of muscle fatigue, depending on the type of muscle and type of stimulation[1]. It can result from failure of AP propagation in the T-system, caused by a build-up of K^+ and consequent depolarization[2]. Using electrically-stimulated skinned muscle fibres[3], we found that intracellular acidification counters this effect by reducing T-system chloride conductance, thus helping prevent the fibre from fatiguing[4]. Muscle fatigue also occurs with repeated stimulation because of effects on the contractile apparatus and, more importantly, a reduction in Ca^{2+} release from the SR[1]. The latter can be due to inorganic phosphate precipitating with Ca^{2+} in the SR, reducing the amount of Ca^{2+} available for rapid release[5,6]. It also seems likely that the fastest contracting fibre types may fatigue because the [ATP] in the cytoplasm drops to very low levels. This decrease, together with the concomitant rise in free [Mg^{2+}] and ATP metabolites, has strong inhibitory effects on the Ca^{2+} release channels, which interferes with their activation by the VS[7]. Finally, repeated increases in cytoplasmic [Ca^{2+}] may cause fatigue lasting more than a day because of Ca^{2+}-dependent damage to the coupling between the VS and the release channels[8], likely due to activation of calpain.

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(7) Dutka & Lamb, J Physiol (In Press), 2004
(8) Lamb et al, J Physiol 489, 349, 1995.