Exciting muscles: ion channels and excitation-contraction coupling in exercise and disease

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A skeletal muscle fibre is a highly specialised excitable cell with a very ordered structure and many 'clever' regulatory mechanisms, which together enable the fibre to synchronously contract throughout its whole length and thickness, time and time again, producing the precise force or movement required, over a brief or a prolonged period as needed. It is some of the exquisite 'design features' and regulatory mechanisms of the ion channels and other processes that allow a muscle fibre to accurately and repeatedly perform its demanding function.

The term 'excitation-contraction coupling' denotes the complex sequence of events in a muscle fibre (Lamb, 2000) encompassing the following: i) initiation of an action potential in the post-synaptic membrane and its propagation along the surface membrane and into the transverse tubular (t-) system ('excitation'); ii) activation of the voltage-sensors (dihydropyridine receptors) in the t-system; iii) opening of the ryanodine receptor-Ca^{2+} release channels (RyRs) in the adjacent sarcoplasmic reticulum (SR) membrane; iv) release of Ca^{2+} stored in the SR; v) increase in the free [Ca^{2+}] in the cytoplasm; vi) binding of Ca^{2+} to regulatory sites on troponin-C; and finally vii) force production by the contractile proteins ('contraction'). This sequence involves the coordinated activation of many different types of ion channels, both voltage-gated and ligand-gated, which depends greatly on their specific characteristics, localization, density and regulatory control.

An interesting question is how the spread of excitation in normal muscle fibres ensures that every region is excited in synchrony without allowing action potentials to re-emerge from the t-system and cause unintended re-excitation (Posterino *et al.*, 2000; Lamb, 2005). Regulation of the Cl^- conductance enables the membrane potential to be stabilised and yet excitability to be preserved in the face of repeated excitation and run-down of the K^+ gradient (Pedersen *et al.*, 2004; Dutka *et al.*, 2008). The regulatory control of the RyRs, in particular by ATP and cytoplasmic Mg^{2+}, is critical to normal voltage-sensor control of Ca^{2+} release (Lamb & Stephenson, 1994; Laver *et al.*, 2001) and also plays a pivotal role in reducing SR Ca^{2+} release in extreme metabolic conditions (Dutka & Lamb, 2004). The latter suggests that the muscle fatigue occurring in some circumstances is possibly simply the consequence of triggering a vital protective mechanism in the cells (Allen *et al.*, 2008). A further important feed-back system operating in muscle regulates the amount of Ca^{2+} released through the RyRs such that an action potential elicits a set amount of Ca^{2+} release irrespective of whether the total amount of Ca^{2+} stored in the SR has increased (Posterino & Lamb, 2003); this helps ensure the muscle fibre produces the desired force response irrespective of any preceding muscle activity. Some of the mechanisms influencing the responsiveness of contractile apparatus can increase as well as decrease responsiveness (Lamb & Posterino, 2003; Murphy *et al.*, 2008).

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