PERSPECTIVES

Combating muscle fatigue: extracellular lactic acidosis and catecholamines

M. I. Lindinger
Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, ON, Canada N1G 2W1

Email:mlinding@uoguelph.ca

During strenuous exercise, contracting skeletal muscle fatigues at a high rate in part due to ionic imbalances occurring across the sarcolemma that contribute to decreased sarcolemmal excitatibility (Sjogaard, 1990). It is suspected that the reduced excitability contributes to a reduction in calcium release by the sarcoplasmic reticulum and a consequent decrease in the force of muscle contraction (Lindinger, 2006). The contribution of this membrane mechanism to the fatigue of high-intensity exercise has been proposed as a way of protecting contracting muscle cells against the damage that may occur if contraction were to continue (Sjogaard, 1990). The accumulation of lactate and especially associated protons, both within the cell and in the extracellular fluids surrounding cells (Lindinger *et al.* 2005), have also long been thought to contribute to the fatigue of high-intensity exercise. However, Nielsen *et al.* (2001) previously raised serious questions about the roles of lactate and acidosis in the fatigue process when they showed, in rat muscle *in vitro*, that acidosis counteracted the effects of increased extracellular $[K^+]$ ($[K^+]_o$) on sarcolemmal V_m. So, while the effects of increased $[K^+]_o$ as a key contributor to the fatigue of high-intensity exercise remain unrefuted, the elevated extracellular $[H^+]$ of exercise appears to allow muscle to continue to contract despite a higher $[K^+]_o$. Further, the authors have gone on to state: 'In many kinds of exercise, reduced excitability may never contribute to fatigue because endogenous protection via activation of the Na^+–K^+ pumps and/or development of acidosis is sufficient to maintain excitability' (Nielsen & Overgaard, 2006). It is noteworthy that other 'protective' effects of lactate on sustaining muscle contraction are also recognized (Brooks, 2001; Cairns, 2006).

In this issue of *The Journal of Physiology*, Nielsen and coworkers (de Paoli *et al.* 2007) provide support that extracellular lactate accumulation has a protective effect on muscle excitability. They demonstrated that an increased extracellular acidity (20 mmol l^{-1} lactic acid), similar to that seen during high-intensity exercise, is additive to the effects of elevated adrenaline on stabilizing membrane excitability. Most importantly, the combination of these two effects was able to fully restore muscle force production. In contrast, adrenaline without concurrent increase in extracellular acidity, through its effects of increasing sarcolemmal Na^+–K^+-ATPase activity and hence membrane potential, was not able to fully restore sarcolemmal excitability or muscle force production.

Limitations of the studies to date is that they have been performed on isolated fibre bundles or fibres, typically at room temperature *in vitro*, and the manipulations performed only mimic a few of the key changes that occur during high-intensity muscle contractions. Another caveat is that the influence of elevated $[H^+]_o$ on fatigue of muscle *in vitro* is pronounced at low temperature but not at physiological temperatures; however, this temperature effect is not pronounced at elevated intracellular $[H^+]$ (Knuth *et al.* 2006). It remains unknown if the mechanisms that operate in such controlled conditions *in vitro* occur to a similar degree within complex *in vivo* systems. In the exercising human, there occur simultaneous changes in both the intra- and extracellular ionic and metabolic environments. So while the *in vitro* studies provide insight as to what may occur, we should still ask the question: Why should we expect the results of the present study to be similar to what occurs in contracting muscle *in vivo*? I am sure that we all look forward to finding out the answers.

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 DOI: 10.1113/jphysiol.2007.132209