PERSPECTIVES

# Muscle fatigue and reactive oxygen species

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Why do muscles fatigue? This is a short and simple question, but the answer is long and complicated. Although muscle fatigue has been investigated for many years, we cannot give a clear description of the underlying mechanisms. The obvious reasons are that it is a multifactorial situation and that the limiting factors may vary with force intensity, exercise duration and muscle type. In this issue of *The Journal of Physiology*, McKenna *et al.* (2006) throw new light on the causal connections.

Muscle fatigue (for review see Fitts, 1994) has been associated with disturbances in $Na^+$–$K^+$ balance, changes in intracellular pH, accumulation of inorganic phosphate, impaired energy metabolism, accumulation of free radical species, and impaired intracellular $Ca^{2+}$ handling and sensitivity. The debate about muscle fatigue has intensified recently. For instance, there has been a controversy about the role of intracellular $H^+$ accumulation (Nielsen *et al.* 2001; Kristensen *et al.* 2005).

Accumulation of reactive oxygen species has been suggested to be a fatigue factor. McKenna and coworkers used an antioxidant compound (NAC, *N*-acetylcysteine) to investigate the effect of reactive oxygen species on fatigue development in well-trained humans. It had been demonstrated already that NAC reduces the level of reactive oxygen species (Medved *et al.* 2003). Human subjects exercised to fatigue on a cycle ergometer and it was observed that infusions of NAC significantly increased the time to fatigue. The study clearly indicates that reactive oxygen species have a role in fatigue. This is by itself a remarkable result. But McKenna *et al.* went further and investigated the underlying mechanisms.

Among the well-known fatigue factors are the disturbances in $Na^+$ and $K^+$ gradients during muscle activity that impair excitability. The underlying mechanism is the inability of the $Na^+$,$K^+$ pump to restore ionic gradients completely during intense exercise. Therefore, the activity of the pump is central to the development of fatigue. To meet its requirements the pump is activated acutely during and after muscle activity by changes in ion affinity, by hormones and by translocation of pump subunits. Although this up-regulation of the pump is expected to improve both the $Na^+$ and $K^+$ homeostasis during muscle activity, changes in concentrations of these ions occur during muscle activity.

It has been demonstrated that the maximal $Na^+$,$K^+$ pump activity ($K^+$-stimulated 3-*O*-methylfluorescein phosphatase; 3-*O*-MFPase) is depressed for a time after intense muscle activity (Fraser *et al.* 2002). This is a mysterious and unexpected effect. It must be noted that the 3-*O*-MFPase method is not the best way to characterize the pump, as the real $Na^+$ and $K^+$ affinities are not determined. However, this method can be used to study changes in pump activity. In the study by McKenna *et al.* infusion of NAC attenuated the decline in maximal pump activity. At the same time, the increase in plasma $K^+$ during exercise was attenuated, which suggest that the NAC-induced effects on the $Na^+$,$K^+$ pump are of functional importance, although it cannot be excluded that NAC might affect other mechanisms. The important finding is that the $Na^+$,$K^+$ pump in muscle is sensitive to reactive oxygen species. This suggests a link between the accumulation of reactive oxygen species and disturbances in the $Na^+$ and $K^+$ balance, and hence a combination of two of the fatigue factors listed above.

Although this study gives us a new connection between some of the underlying factors in fatigue, it also raises new questions. What is the mechanism for the inhibitory effect of reactive oxygen species on the $Na^+$,$K^+$ pump? How is this effect preserved in muscle biopsies homogenized and prepared for the 3-*O*-MFPase measurements? Answers to these questions will teach us more about this new and important regulation of the $Na^+$,$K^+$ pump.

The paper also raises another series of ethical and legal questions to be discussed in another forum. Is it a good idea for athletes to take antioxidants to enhance performance? Will this be considered to be doping?

## References

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