Iron accelerates skeletal muscle fatigue at 37°C

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The loss of muscle performance during intense or prolonged muscular activity is known as fatigue, and is common in disease states like heart failure. Many factors are thought to contribute to muscle fatigue including a decrease in energy stores and an increase in metabolic by products such as reactive oxygen species (ROS). Recent work from our laboratory has shown that muscle fatigue is accelerated at 37°C due to a loss in calcium sensitivity, which can be prevented by the ROS scavenger Tiron (Moopanar & Allen, 2005) or reversed by the reducing agent DTT (Moopanar & Allen, 2006).

Iron can accelerate the production of the hydroxyl radical ($OH^{\bullet}$) through the Fenton reaction. Given that even the typical gauge 22 metal needle syringe can introduce significant amounts of iron into solution (Buettner, 1990), this study explored the role of iron in muscle fatigue at 37°C.

Small muscle bundles (2-6 fibres) were isolated from the mouse foot after rapid cervical dislocation. Muscles were fatigued (force reduced to 50%) by repeated short tetani at room temperature, allowed to recover, and fatigued again at 37°C. The time taken to fatigue at 37°C was then normalized to the room temperature fatigue run for analysis. Solutions were heated to 37°C by an insulated heat exchange system consisting of either aluminium or stainless steel piping. Both a non specific (100μM EGTA), and specific iron chelator (250nM-200μM desferrioxamine) were used in separate experiments to bind iron and inhibit Fenton reactions.

Time taken to fatigue at 37°C was reduced to 68% ± 10 (n = 6) of the initial fatigue run at room temperature, using the stainless steel heat exchanger. The accelerated fatigue at 37°C was prevented by the addition of EGTA (106% ± 16, n = 5) and desferrioxamine (108% ± 12, n = 6). No acceleration in fatigue time was observed using the aluminium heat exchanger (125% ± 8, n = 7).

Based on previous work from this laboratory, the accelerated fatigue observed at 37°C using a stainless steel heat exchanger is due to decreased Ca^{2+} sensitivity mediated through ROS. As iron can accelerate the production of $OH^{\bullet}$, and the metal chelators EGTA and desferrioxamine can prevent the accelerated fatigue, it appears likely iron is producing the $OH^{\bullet}$ and is contributing to the accelerated fatigue under these conditions.

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Moopanar TR & Allen DG. (2005) *Journal of Physiology*, **564:** 189-99.
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