The peak tetanic force-$[K^+]_o$ relationship in mouse fast- and slow-twitch muscle: modulation with $[Na^+]_o$ or $[Ca^{2+}]_o$

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Potassium (K^+) is frequently postulated to cause skeletal muscle fatigue. Indeed, the trans-sarcolemmal K^+ gradient falls during high-intensity exercise (Sejersted & Sjøgaard, 2000) and experimentally raising extracellular $[K^+]$, ($[K^+]_o$) causes depolarisation and reduces force in non-fatigued muscle (Cairns *et al.*, 1997, 1998). However, large elevations of $[K^+]_o$ are necessary to cause a severe reduction of force (Cairns *et al.*, 1997). The aim of the present study was to extend our understanding of the role of K^+ in fatigue, by testing for interactive effects between raised $[K^+]_o$ and other ionic changes that occur during intense exercise (Cairns *et al.*, 1998; Sejersted & Sjøgaard, 2000), i.e., diminished trans-sarcolemmal sodium (Na^+) and calcium (Ca^{2+}) gradients.

Isometric contractions were evoked by supramaximal electric field stimulation (parallel plate electrodes) in isolated slow-twitch soleus (SOL) or fast-twitch extensor digitorum longus (EDL) muscles of mice. Muscles were bathed in control Krebs solution (4 mM K^+, 147 mM Na^+, 1.3 mM Ca^{2+}, 128 mM Cl^-) at 25°C. With raised K^+ solutions NaCl was replaced with KCl, with lowered Na^+ solutions NaCl was replaced with N-methyl-D-glucamine, and with altered Ca^{2+} solutions Ca^{2+} was replaced with Mg^{2+}, or $CaCl_2$ was added. Maximum tetanic force was achieved at 125 Hz in SOL and 200 Hz in EDL. Fatigue was induced with repeated tetanic stimulation at 125 Hz for 500 ms, every 1 s, for 100 s.

When $[K^+]_o$ was raised from 4 to 7 mM fatigue was exacerbated, and when $[K^+]_o$ was lowered to 2 mM the fatigue was slowed in SOL. The relative force at 100 s of stimulation (mean value) was 50% initial at 2 mM K^+, 40% at 4 mM K^+, and 23% at 7 mM K^+. The relationship between peak tetanic force and $[K^+]_o$ (8-12 mM) was established in non-fatigued muscles. At raised $[K^+]_o$ (i) increasing the stimulation pulse strength (20 to 26 V) increased force in SOL but not EDL, (ii) increasing the stimulation pulse duration (0.1 to 0.15 to 0.25 ms) progressively restored force, but to a greater extent in SOL than EDL, and (iii) stimulating with transverse wire rather than parallel plate electrodes resulted in a greater force loss, especially in SOL. When $[K^+]_o$ was raised to 8 mM and $[Na^+]_o$ lowered to 100 mM, synergistic depressive effects occurred on peak tetanic force in both SOL and EDL, i.e., the peak tetanic force-$[K^+]_o$ relationship shifted leftwards towards lower $[K^+]_o$. Force could then be partially restored by lowering the stimulation frequency but only in SOL. Raising the $[Ca^{2+}]_o$ (1.3 to 2.5 to 10 mM) shifted the peak tetanic force-$[K^+]_o$ relationship in SOL rightwards towards higher $[K^+]_o$. Conversely, lowering $[Ca^{2+}]_o$ shifted the relationship leftwards, e.g., at 8 mM K^+ the peak force was 77% initial at 1.3 mM Ca^{2+} and 52% initial at 0.5 mM Ca^{2+}.

In summary, moderate changes of $[K^+]_o$ clearly influence the rate of fatigue in SOL which implicates K^+ in the fatigue process. The peak tetanic force-$[K^+]_o$ relationship in non-fatigued muscle depended on the stimulation pulse parameters and stimulation electrode type, and more so in SOL than EDL. Muscles are more susceptible to K^+-induced force depression at slightly lowered $[Na^+]_o$ and slightly lowered $[Ca^{2+}]_o$ which is a likely physiological scenario. Thus, when such ionic shifts occur simultaneously during exercise, they are likely to act together to impair muscle force production, i.e., cause fatigue.

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