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## The Changes of $[Ca^{2+}]$ in Sr and $Ca^{2+}$ Release Flux during Fatiguing Activation of Mouse Skeletal Muscle Fibers

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# The Changes of $[Ca^{2+}]$ in Sr and $Ca^{2+}$ Release Flux during Fatiguing Activation of Mouse Skeletal Muscle Fibers

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Sustained activity leads to muscle fatigue, cellular correlates of which include depression in  $Ca^{2+}$  released per action potential (Györke, *JPhysiol*, 1993; Westerblad, *JAppPhysiol*, 1993). This decrease is also observed in cells activated with voltage clamp pulse trains (Royer, *JGP*, 2010), which points at effectors downstream from the voltage sensor, including depletion of SR  $Ca^{2+}$  (Allen, *JAppPhysiol*, 2011). In mouse FDB cells expressing the

biosensor D4cpv-calsequestrin loaded with X-rhod1-AM or in mice constitutively expressing the troponin-based FRET biosensor TnXX (Mank, NatureM, 2008) we measure  $[Ca^{2+}]_{SR}$ ,  $[Ca^{2+}]_{cyto}$  and release flux. Fatiguing activation is produced by 0.5s trains of action potentials at 2s intervals. Concentrations were measured before the tetanus (*rest*) or at its end (*tet*) in the rested condition ( $t_0$ ), upon 1 or 3 min of stimulation ( $t_1, t_3$ ) and after 10 min recovery (A10). Flux was calculated as amount released/tetanus duration. Further analysis of this quantitative picture of  $Ca^{2+}$  handling during fatigue indicates that the reduction in  $Ca^{2+}$  release is the outcome of interconnected decreases in SR load,  $Ca^{2+}$  release permeability and SR  $Ca^{2+}$  buffering power.

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$t_0$	$t_1$	$t_3$	A10	
$[Ca^{2+}]_{cyto, rest}, nM$	80	127	162	117
$[Ca^{2+}]_{cyto, tet}, nM$	250	254	234	187
flux, mM/s	1.32	1.09	0.58	0.72
$\Delta$ amount, mM	0.53	0.46	0.27	0.30
$[Ca^{2+}]_{SR, rest}, \mu M$	290	245	240	280
$[Ca^{2+}]_{SR, tet}, \mu M$	210	195	195	205