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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 (t0), upon 1 or 3 min of stimulation (t1,t3) 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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t0	t1	t3	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
Δ amount, mM	0.53	0.46	0.27	0.30
$[Ca^{2+}]_{SR,rest,}$ μM	290	245	240	280
$[Ca^{2+}]_{SR,tet,}$ μM	210	195	195	205