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Down and Out. The Functional Effects of Silencing Calsequestrin 1 or Deleting Both Calsequestrin Genes In Mammalian Muscle

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Calsequestrins 1 and 2 are major calcium binding proteins of the SR in skeletal and cardiac muscle. We transiently suppressed synthesis of CSQ1 in fast twitch muscle of live adult mice by transfection with a plasmid coding for siRNA and a marker. Immunoblots showed reduction of CSQ1 by 40 to 100% in the whole treated (FDB) muscle. Ca^{2+} transients and Ca^{2+} release flux were measured in fibers selected for their high expression of the marker and patch clamped. Similar studies were done with FDB fibers from a double-null strain created by crossing CSQ1-null (Paolini et al. 2007) with CSQ2-null mice (Knollmann et al. 2006). Total Ca^{2+} releasable by maximal prolonged depolarization was decreased by up to 30% in silenced and 40% in KO muscles compared with the wild type. The reduction in CSQ had subtle kinetic consequences. The time course of release flux induced by long depolarization lost a “shoulder” (present in the WT; Royer et al. 2008). This shoulder reflects a component of the SR Ca^{2+} buffering power characterized by its dependence on $[Ca^{2+}]_{SR}$. Its loss here identifies the shoulder as a kinetic signature of the presence of CSQ. The KO presents additional anomalies, including asynchronous activation of different regions, and, occasionally, abnormally high initial release flux. Both features may be associated with structural changes like those found in the CSQ1 KO (Paolini, 2007). In conclusion, muscle either transiently or permanently devoid of CSQ is still capable of releasing large quantities of Ca^{2+}. Means of Ca^{2+} storage unrelated to CSQ appear to play a major role in skeletal muscle. Supported by NIAMS/NIH.