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RESEARCH NEWS

# Small calcium leaks, big muscle adaptations

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***JGP* study finds that mild calcium leak is associated with improved resistance to muscle fatigue.**

Muscle training results in muscle adaptations that increase both performance and resistance to fatigue, whereas overtraining can result in muscle weakness. Muscle weakness also appears alongside various diseases such as muscular dystrophies and rheumatoid arthritis. A better understanding of the pathways affecting muscle adaptation could therefore lead to major improvements in both disease settings and athletic performance. A *JGP* paper by Ivarsson et al. uncovers a pathway that increases muscle fatigue resistance (1).

"With endurance exercise, the muscle adapts so you can perform a task better," says Johanna Lanner, an Assistant Professor at the Karolinska Institutet in Stockholm, Sweden. Exercised muscle contains more mitochondria, demonstrating increased mitochondrial mass and the expression of genes involved in mitochondrial biogenesis, such as PGC1α1 (2). "We wondered, 'How can a contracting muscle lead to more mitochondria?'"

During each muscle contraction,calcium ions ($Ca^{2+}$) are released from the sarcoplasmic reticulum into the cytoplasm. There, $Ca^{2+}$ enables interaction between myosin motors and actin thin filaments to produce shortening of muscle filaments, and then it is returned to the sarcoplasmic reticulum by the SERCA $Ca^{2+}$ pump. $Ca^{2+}$ release from the sarcoplasmic reticulum is controlled by the ryanodine receptor (RyR1), a giant protein whose stability is regulated by a subunit called FKBP12 (3).

"If FKBP12 is not there, you get an unstable receptor that turns leaky," explains Lanner. "Such leak has always been considered something bad that contributes to muscle weakness."

Extreme RyR1 leakiness causing prolonged elevations in cytoplasmic $Ca^{2+}$ is observed both in disease settings (4) and during muscle overtraining (5). However, recent work hints that lower levels of RyR1 $Ca^{2+}$ leak might actually be beneficial (6). Because $Ca^{2+}$ is a potent second messenger, Ivarsson and colleagues hypothesized that exercise training may provoke changes in baseline cytoplasmic $Ca^{2+}$ levels, thereby changing gene expression or other processes. To probe this, the researchers gave mice access to running wheels and examined how exercise affects $Ca^{2+}$ leak, baseline cytoplasmic $Ca^{2+}$, and muscle mitochondria.


First author Niklas Ivarsson (left), co-senior authors Johanna Lanner (center) and Håkan Westerblad (not shown), and colleagues found that mild $Ca^{2+}$ leak through ryanodine receptors correlates with increased expression of markers for mitochondrial biogenesis (graph, right) and improved muscle function. Sadly, Ivarsson passed away on October 10, 2018. Photos courtesy of the authors.

After three weeks of voluntary exercise, mouse skeletal muscle displayed higher levels of FKBP12 dissociation from RyR1 and 25% higher baseline $Ca^{2+}$ concentrations. This was accompanied by a marked increase in expression of PGC1α1 and other genes involved in mitochondrial biosynthesis. By six weeks of exercise, however, the period of muscle adaptation had ended; mitochondrial content was higher, PGC1α1 gene expression and FKBP12 dissociation had returned to normal, expression of SERCA protein had increased, and baseline $Ca^{2+}$ concentration was back to its original level.

The strong correlation between RyR1 leakiness and expression of mitochondrial biogenesis markers prompted Ivarsson et al. to investigate whether inducing a mild $Ca^{2+}$ leak with pharmacological agents might prompt muscle adaptation. They found that muscle injected periodically over three weeks with low levels of the drug rapamycin, which binds FKBP12 and forces its dissociation from RyR1, exhibited similar levels of baseline $Ca^{2+}$ and mitochondrial biosynthesis as exercised muscle. Rapamycin-treated muscle also showed functional improvements compared with muscle from rested mice.

"It appears that a small RyR1 $Ca^{2+}$ leak can be a trigger for signaling pathways that improve fatigue resistance in muscle. We want to investigate the molecular mechanisms involved," says Lanner. And, she adds, if it works the same in humans as in mice, a pharmacological pathway providing a shortcut to improved muscle function could help patients suffering muscle weakness due to disease, or athletes training their muscles. Although it could be dangerous to use rapamycin for this purpose because the drug can cause severe immunosuppression and cardiac arrest, future work might produce a safer route.

1. Ivarsson, N., et al. 2019. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.201812152
2. Baar, K., et al. 2002. *FASEB J.* 16:1879–1886.
3. Ahern, G.P., et al. 1997. *Neurosci. Lett.* 225:81–84.
4. Bellinger, A.M., et al. 2009. *Nat. Med.* 15:325–330.
5. Bellinger, A.M., et al. 2008. *Proc. Natl. Acad. Sci. USA.* 105: 2198–2202.
6. Lee, C.S., et al. 2014. *J. Biol. Chem.* 289:25556–25570.

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