Journal of General Physiology

RESEARCH NEWS

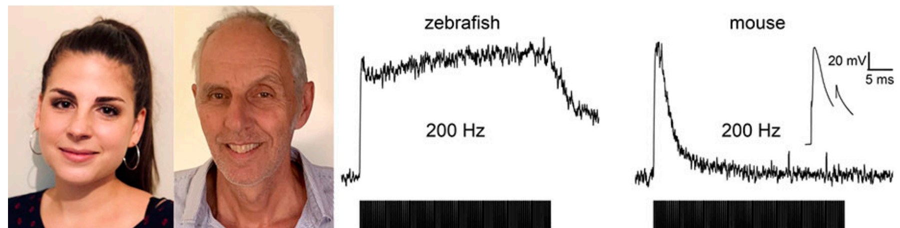
Excitation–Contraction Coupling

Superfast fish show superfast coupling

Ben Short

JGP study reveals that adult zebrafish skeletal muscle fibers display the fastest kinetics of excitation–contraction coupling ever measured in vertebrate locomotor muscles.

The nervous excitation of vertebrate skeletal muscle fibers is coupled to muscle contraction by a series of events in which action potentials propagate along the muscle membranes and trigger conformational changes in voltage-sensitive dihydropyridine receptors (DHPRs) that, via a direct interaction with ryanodine receptors, cause Ca^{2+} to be released from the sarcoplasmic reticulum. To date, the fastest excitation–contraction (EC) coupling kinetics ever recorded have been in the muscle fibers of male toadfish swim bladders, which, rather than generating movement, produce the sound of the animal's mating call (1). In this issue of *JGP*, however, Idoux et al. (2) describe similarly rapid EC coupling in the locomotor muscles of adult zebrafish.



Romane Idoux (left), Bruno Allard (center), and colleagues demonstrate the superfast kinetics of EC coupling in adult zebrafish skeletal muscle fibers that allow the muscles to contract when excited at extremely high frequencies, powering the animal's rapid startle response. When stimulated at 200 Hz for 0.5 s, zebrafish fibers form a fused and sustained Ca^{2+} transient (left trace), whereas in a mouse fiber excited at the same rate (right trace), the initial Ca^{2+} transient quickly returns to baseline because the second stimulation of the train fails to trigger an action potential (inset).

Zebrafish have a strong startle response that allows them to escape predators and catch prey. This rapid swimming activity is driven by fast muscle fibers that display superfast contraction kinetics, generating fused, tetanic contractions at extremely high frequencies of excitation not seen in mammalian skeletal muscles (3). These superfast kinetics depend, in part, on the properties of contractile proteins in the zebrafish muscle sarcomeres. But they likely also require superfast EC coupling kinetics.

"However, although EC coupling has been measured in zebrafish fast skeletal muscle cells, there has been no attempt to compare the kinetics with mammalian fast fibers," explains Bruno Allard, whose research group at the Université Claude Bernard Lyon 1 studies adult zebrafish as a model for human muscular disease.

Allard and colleagues, including first author Romane Idoux, isolated fast muscle fibers from adult zebrafish and mice, and performed a series of voltage- and current-clamp experiments combined with intracellular Ca^{2+} measurements to monitor the different steps of EC coupling (2).

First, the researchers compared the action potentials generated in these fibers and found that zebrafish action potentials have a smaller amplitude and repolarize much faster than those seen in mouse muscle fibers. Allard and colleagues speculate that this rapid repolarization, which allows zebrafish muscles to be stimulated at frequencies of almost 200 Hz, could be driven by the Ca^{2+}-activated chloride channel ANO1, which is absent from mammalian muscle but has been shown to accelerate action potentials in zebrafish larval muscle cells (4).

Idoux et al. (2) saw similarly rapid kinetics when they measured the intramembrane charge movements associated with DHPR activation. This voltage-dependent step occurred up to four times faster in zebrafish than it does in mice, possibly due to species-specific differences in DHPR and its four voltage-sensing domains. Mouse DHPR is a calcium channel whose opening is controlled by one, slowly activating voltage-sensing domain (5). Zebrafish DHPR, in contrast, does not conduct calcium, potentially allowing all four of its voltage-sensing domains to control the rapid activation of ryanodine receptors.

Correspondence to Ben Short: bshort@rockefeller.edu

This work is part of a special issue on excitation–contraction coupling.

© 2022 Rockefeller University Press. This article is distributed under the terms of an Attribution–Noncommercial–Share Alike–No Mirror Sites license for the first six months after the publication date (see http://www.rupress.org/terms/). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 4.0 International license, as described at https://creativecommons.org/licenses/by-nc-sa/4.0/).

Check for updates

Finally, Idoux et al. (2) measured the intracellular Ca^{2+} transients arising from ryanodine receptor activation. These, too, showed superfast kinetics in zebrafish muscle fibers, with decay rates much faster than those seen in mice, likely due to increased density of a high affinity intracellular Ca^{2+} buffer, probably parvalbumin, as shown by a Ca^{2+} distribution model simulating Ca^{2+} transients built by the authors.

Together, these superfast kinetics of EC coupling allowed adult zebrafish muscle fibers to form fused and sustained Ca^{2+} transients at excitation frequencies of ~200 Hz, similar to the high fusion frequencies previously observed in toadfish swim bladder muscles (1). In contrast, with their slower decay rates, Ca^{2+} transients in mouse muscle fibers fuse at much lower excitation frequencies, and cannot be sustained at 200 Hz as the slow kinetics of action potential repolarization cause the muscle membranes to become refractory.

"To our knowledge, our study is the first demonstration of superfast EC coupling properties in vertebrate skeletal muscles involved in locomotion," Allard says. "The accelerated kinetics of each EC coupling step enable the superfast contraction kinetics of zebrafish fast muscle fibers that are known to be involved in the animal's startle response."

References

1. Rome, L.C., et al. 1996. *Proc. Natl. Acad. Sci. USA*. https://doi.org/10.1073/pnas.93.15.8095
2. Idoux, R., et al. 2022. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.202213158
3. Dou, Y., et al. 2008. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.200809982
4. Dayal, A., et al. 2019. *Nat. Commun.* https://doi.org/10.1038/s41467-018-07918-z
5. Savalli, N., et al. 2021. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.202112915