JGP Journal of General Physiology

RESEARCH NEWS

Skeletal muscle gets some help down the stretch

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JGP study (Woods et al. https://doi.org/10.1085/jgp.202413679) suggests that stretch activation of fast-contracting skeletal muscle fibers might increase muscle endurance by boosting force production during fatigue.

Stretch activation is a delayed increase in tension that can be observed in many types of muscle fibers after they are lengthened. This can benefit muscle performance if the stretch-activated tension develops during subsequent muscle shortening, boosting the total amount of force produced by the fiber. The phenomenon is not thought to make a significant contribution to skeletal muscle function under normal conditions. In this issue of *JGP*, however, Woods et al. suggest that stretch activation could become important in fatigued skeletal muscle when stretch-activated tension persists even as regular, calcium-activated force production declines (1).

Stretch-activated tension is the main contributor to force generation in the indirect flight muscles of fruit flies and other insects, where antagonistic muscle pairs undergo rapid cycles of lengthening and shortening to power the insect's wing movements (2). It also makes a significant contribution to force production in vertebrate cardiac muscle (3). But in skeletal muscle, stretch activation produces only a tenth of the force that can be induced upon maximal Ca^{2+} activation, suggesting that it has no physiological role in this type of muscle (4).

"Recently, however, we found that, when we increased inorganic phosphate levels in skeletal muscle, we saw a bigger stretch-activated response," says Mark Miller, an associate professor at UMass Amherst, referring to a study (5) performed in collaboration with Douglas Swank's group at the Rensselaer Polytechnic Institute.

This led Miller and colleagues to wonder whether stretch-activated tension could become physiologically significant when skeletal muscle fatigues, a situation in which inorganic phosphate (P_i) accumulates within muscle fibers. This accumulation is accompanied by a decrease in pH and a reduction in isometric force production. Eventually, fatigue disrupts Ca^{2+} handling within fibers, inhibiting force production even further.

Miller and colleagues, led by graduate student Philip Woods, therefore measured the stretch activation response in mouse skeletal muscle fibers exposed to P_i, H^+, and Ca^{2+} concentrations mimicking either active, early fatigue, or late fatigue conditions. Because the response can be influenced by myosin subtype (5, 6), the researchers also carefully determined the myosin heavy chain (MHC) isoform expressed by each of the tested fibers.

Woods et al. saw only a small stretch activation response in slow-contracting (MHC I) fibers under active conditions, and no response at all under fatiguing conditions. In fast-contracting (MHC IIA, IIB, or IIX) fibers, however, the researchers observed a relatively large stretch activation response under active conditions, and this response either increased or remained unchanged in fatigue-mimicking solutions. Thus, because Ca^{2+}-activated tension declines as muscles fatigue, the contribution of stretch-activated tension to total force production increases as fast-contracting fibers grow tired.

"We think this makes sense because P_i and H^+ accumulate much more quickly in fast-contracting fibers than in slow-contracting fibers, so they may have evolved to be more sensitive to stretch activation," Miller says. By partially compensating for the decline in Ca^{2+}-activated tension as fast-contracting fibers fatigue, stretch activation may therefore increase the endurance of muscles that undergo cycles of lengthening and shortening, such as those that power running and swimming.

Philip Woods, Douglas Swank, and Mark Miller.

The researchers now plan to investigate the mechanism underlying the stretch activation response during fatigue. One possibility is that, when muscles with elevated P_i levels are stretched, P_i rebinds to myosin-ADP crossbridges that have undergone a power stroke and are strongly attached to actin. The rebinding of P_i converts these crossbridges back into a weakly attached, pre-power stroke state, allowing them to undergo a second power stroke without an additional round of ATP binding and hydrolysis. Miller and colleagues also want to explore in more detail how the contribution of stretch-activated tension changes during mild and high-intensity exercise.

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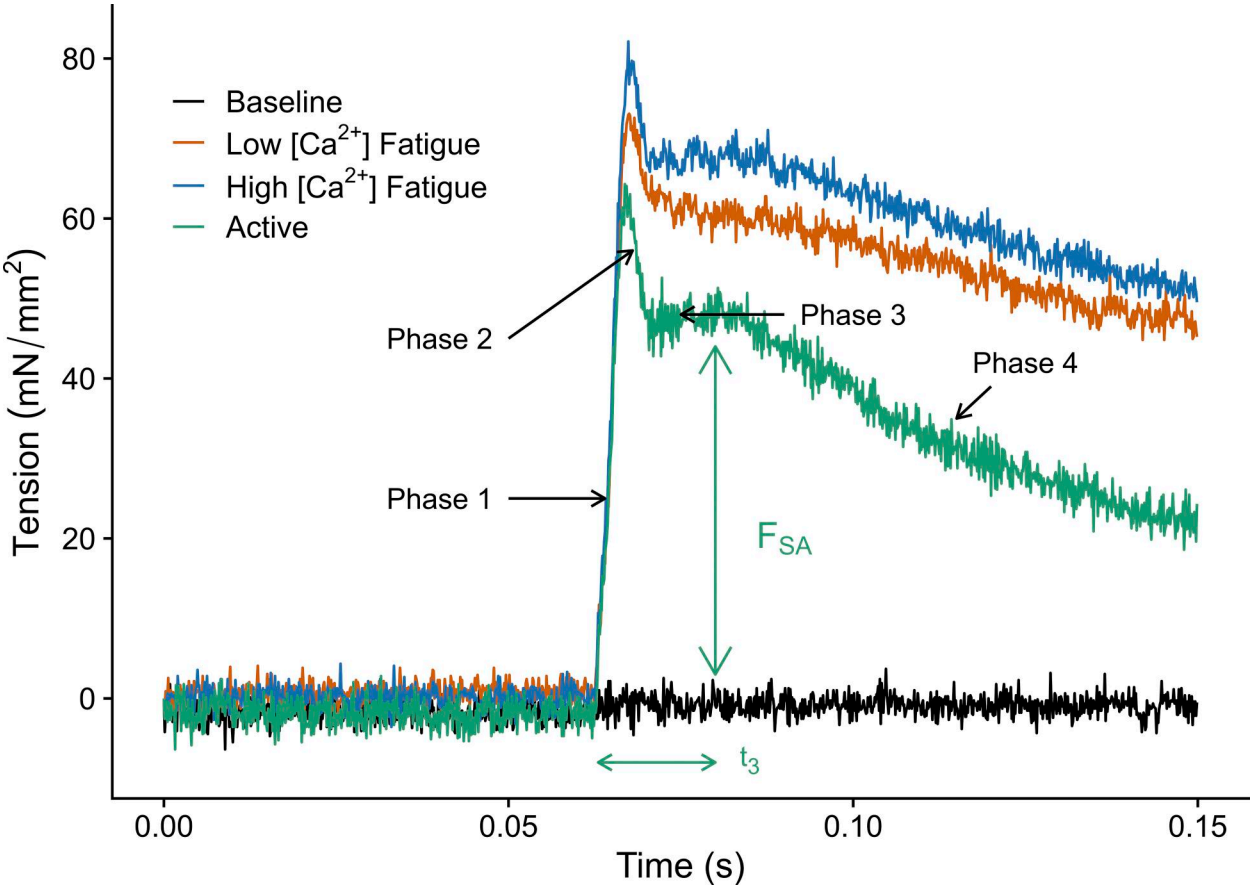

Woods et al. reveal that stress-activated tension (F_{SA}) remains unchanged or increases in fast-contracting skeletal muscle fibers exposed to fatiguing conditions, as shown in these representative raw force traces of a stretched mouse MHC IIX–expressing fiber. Because Ca^{2+}-activated isometric tension declines in response to fatigue, F_{SA} makes a significant contribution to total force production under fatiguing conditions, potentially boosting skeletal muscle endurance.

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