

# Researchers show leaky muscle cells lead to fatigue

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What do marathoners and heart failure patients have in common? More than you think according to new findings by physiologists at Columbia University Medical Center.

The new study shows that the fatigue that marathoners and other extreme athletes feel at the end of a race is caused by a tiny leak inside their muscles that probably also saps the energy from patients with heart failure.

The leak – which allows calcium to continuously leak inside muscle cells – weakens the force produced by the muscle and also turns on a protein-digesting enzyme that damages the muscle fibers. The new study found the leak was present in the muscle of mice after an intense three-week daily swimming regimen and in human athletes after three days of daily intense cycling. The same leak was previously discovered by Marks and colleagues in the muscles of animals with heart failure.

The new study also found that an experimental drug developed by the researchers alleviated muscle fatigue in mice after exercise, suggesting that the drug also may provide relief from the severe exhaustion that prevents patients with chronic heart failure from getting out of bed or fixing dinner.

The results will be published in the online edition of the *Proceedings of the National Academy of Sciences* on February 11, 2008.

“The study does not mean exercise is bad for you,” says the study’s senior author, Andrew Marks, M.D., chair of the Department of Physiology and Cellular Biophysics, and director of the Clyde and Helen Wu Center for Molecular Cardiology at Columbia University Medical Center. “We only saw the leak in animals and human athletes that exercised three hours a day at very high intensities for several days or weeks in a row until they were exhausted.” He notes that athletes’ muscles also will return to normal after several days of rest and any muscle damage will be repaired after several days or weeks depending on the degree of exercise.

However, the arm, leg and breathing muscles of patients with heart failure never have a chance to recover. “People with chronic heart failure are subject to this same kind of muscle leak and damage constantly even without doing any exercise,” Marks says. “One of these patients’ most debilitating symptoms is muscle weakness and fatigue, which can be so bad they can’t get out of bed, brush their teeth, or feed themselves.”

This fatigue experienced by heart failure patients does not stem from a reduction in the amount of blood and oxygen supplied to the muscles by the heart, as one might expect. Instead, Marks’ previous research in muscles of mice with heart failure suggested that fatigue in patients stems from the calcium leak, which reduced the ability of a single muscle to contract repeatedly before losing force.

“We then had a hunch that the process that produces fatigue in heart failure patients also may be responsible for the fatigue felt by athletes after a marathon or extreme training,” says the study’s first author, Andrew Bellinger, Ph.D., who is currently finishing his M.D. at Columbia University’s College of Physicians & Surgeons. “Our new paper shows that fatigue in both patients and athletes probably stems from the same leak.”

## **Fatigue Can Be Alleviated With Experimental Drug**

The researchers then used the similarity between athletes and patients to their advantage to see if an experimental drug could increase exercise capacity and reduce fatigue.

The researchers gave the drug – which plugs the leak of calcium – to mice before the animals started a 3-week regimen of swimming. Without the drugs, mice are exhausted after three weeks of daily 3-hour swims. With the drug, the mice were still energetic, had lost less exercise capacity after 3 weeks, and their muscles showed fewer signs of calcium leakage, atrophy, and less muscle damage.

The cyclists in the current study were not given the drug, which is not yet available for people.

Plans are underway to test the drug at other medical centers in patients with heart failure to see if it relieves fatigue and improves heart function. Even if successful, it will take several years before the drug will be commercially available.

## **Study Also Provides Explanation for Muscle Fatigue Besides Lactic Acid**

The calcium leak also provides a new explanation for the muscle soreness and fatigue that marathoners and other athletes can experience for weeks after crossing the finish line.

Physiologists have recently largely discarded the 100 year-old theory that lactic acid accumulation in the muscle cells produces fatigue and limits athletic performance. New theories have been exploring the role of calcium in this process. The involvement of defects in calcium handling

in limiting muscle performance and producing exercise fatigue makes sense because the flow of calcium in and out of the muscle cell controls muscle contraction.

The discovery of the calcium leak in fatigued animals and athletes is the first time anyone has pinpointed a precise mechanism for the involvement of a defect in calcium handling in limiting exercise capacity.

Source: Columbia University Medical Center

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