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Finding May Solve Riddle of Fatigue in Muscles

By [GINAKOLATA](#)

One of the great unanswered questions in physiology is why muscles get tired. The experience is universal, common to creatures that have muscles, but the answer has been elusive until now.

Scientists at Columbia say they have not only come up with an answer, but have also devised, for mice, an experimental drug that can revive the animals and let them keep running long after they would normally flop down in exhaustion.

For decades, muscle fatigue had been largely ignored or misunderstood. Leading physiology textbooks did not even try to offer a mechanism, said Dr. Andrew Marks, principal investigator of the new study. A popular theory, that muscles become tired because they release lactic acid, was discredited not long ago.

In a report published Monday in an early online edition of Proceedings of the National Academy of Sciences, Dr. Marks says the problem is [calcium](#) flow inside muscle cells. Ordinarily, ebbs and flows of calcium in cells control muscle contractions. But when muscles grow tired, the investigators report, tiny channels in them start leaking calcium, and that weakens contractions. At the same time, the leaked calcium stimulates an enzyme that eats into muscle fibers, contributing to the muscle exhaustion.

In recent years, says George Brooks of the University of California, Berkeley, muscle researchers have had more or less continuous discussions about why muscles fatigue. It was his work that largely discredited the lactic-acid hypothesis, but that left a void.

What did make muscles tired?

The new work in mice, Dr. Brooks said, "is exciting and provocative." It is a finding that came unexpectedly from a very different line of research. Dr. Marks, a cardiologist, wanted to discover better ways to treat people with [congestive heart failure](#), a chronic and debilitating condition that affects an estimated 4.8 million Americans.

Its hallmark is a damaged heart, usually from a [heart attack](#) or [high blood pressure](#). Struggling to pump blood, the heart grows, sometimes becoming so large that it fills a patient's chest. As the disease progresses, the lungs fill with fluid. Eventually, with congested lungs and a heart that can barely pump, patients become so short of breath that they cannot walk across a room. Half die within five years.

In his efforts to understand why the heart muscle weakened, Dr. Marks focused on the molecular events in the heart. He knew the sequence of events. As the damaged heart tries to deal with the body's demands for blood, the nervous system floods the heart with the fight or flight hormones, [epinephrine](#) and norepinephrine, that make the heart muscle cells contract harder.

The intensified contractions, Dr. Marks and his colleagues discovered, occurred because the hormones caused calcium to be released into the heart muscle cells' channels.

But eventually the epinephrine and norepinephrine cannot stimulate the heart enough to meet the demands for blood. The brain responds by releasing more and more of those fight or flight hormones until it is releasing them all the time. At that point, the calcium channels in heart muscle are overstimulated and start to leak.

When they understood the mechanisms, the researchers developed a class of experimental drugs that block the leaks in calcium channels in the heart muscle. The drugs were originally created to block cells' calcium channels, a way of lowering [blood pressure](#).

Dr. Marks and his colleagues altered the drugs to make them less toxic and to rid them of their ability to block calcium channels. They were left with drugs that stopped calcium leaks. The investigators called the drugs rycals, because they attach to the ryanodine receptor/calcium release channel in heart muscle cells. The investigators tested rycals in mice and found that they could prevent heart failure and [arrhythmias](#) in the animals. Columbia obtained a patent for the drugs and licensed them to a start-up company, Armgo Pharma of New York. Dr. Marks is a consultant to the company.

It hopes to start testing one of the drugs for safety in patients in the spring, but the tests will not be at Columbia because of the university and investigators' conflicts of interest. In the meantime, Dr. Marks wondered whether the mechanism he discovered might apply to skeletal muscle as well as heart muscle. Skeletal muscle is similar to heart muscle, he noted, and has the same calcium channel system. And heart failure patients complain that their muscles are extremely weak.

"If you go to the hospital and ask heart failure patients what is bothering them, they don't say their heart is weak," Dr. Marks said. "They say they are weak."

So he and his colleagues looked at making mice exercise to exhaustion, swimming and then running on a treadmill. The calcium channels in their skeletal muscles became leaky, the investigators found. And when they gave the mice their experimental drug, the animals could run 10 to 20 percent longer.

Then, collaborating with David Nieman, an exercise scientist at Appalachian State University in Boone, N.C., the investigators asked whether the human skeletal muscles grew tired for the same reason, calcium leaks.

Highly trained bicyclists rode stationary bikes at intense levels of exertion for three hours a day three days in a row. For comparison, other cyclists sat in the room but did not exercise.

Dr. Nieman removed snips of thigh muscle from all the athletes after the third day and sent them to Columbia, where Dr. Marks's group analyzed them without knowing which samples were from the exercisers and which were not. The results, Dr. Marks said, were clear. The calcium channels in the exercisers leaked. A few days later, the channels had repaired themselves. The athletes were back to normal.

Of course, even though Dr. Marks wants to develop the drug to help people with congestive heart failure, hoping to alleviate their fatigue and improve their heart functions, athletes might also be tempted to use it if it eventually goes to the market.

The odds are against this particular drug being approved, though, cautions Dr. W. Robb McClellan, a heart disease researcher at U.C.L.A.

"In heart failure, there are three medications that improve mortality, but there have probably been 10 times that many tested," he said.

Even if the first drug that prevents calcium leaks does not work in patients, Dr. McClellan added, the important advance is to understand the molecular events underlying fatigue. "Then," he said, "you can design therapies."

So the day may come when there is an antifatigue drug.

That idea, "is sort of amazing," said Dr. Steven Liggett, a heart-failure researcher at the [University of Maryland](#). Yet, Dr. Liggett said, for athletes "we have to ask whether it would be prudent to be circumventing this mechanism."

"Maybe this is a protective mechanism," he said. "Maybe fatigue is saying that you are getting ready to go into a danger zone. So it is cutting you off. If you could will yourself to run as fast and as long as you could, some people would run until they keeled over and died."

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