
EXERCIS

SE IN A PILL?

Not Quite. But toying with metabolism's machinery might lead to obesity-fighting drugs that bolster the effects of a workout.

by **R. JOHN DAVENPORT**
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In today's typical family, the whirl of work, school, extracurricular activities, and driving, driving, driving leaves little time for sitting down to a healthy meal—and even less time for serious exercise. It's no wonder that obesity and diabetes have reached epidemic proportions.

In response, scientists are delving into the genes and proteins that control the flow of energy in our bodies, and they're making surprising connections to exercise. Their findings could lead to drugs that fight diabetes and obesity by mimicking a vigorous workout.

Just as the government stockpiles and releases gasoline reserves according to demand, our bodies store and mobilize energy to meet our needs—making it available to muscles when we're active and hoarding it when food is scarce. Normally, we control metabolism exquisitely, maintaining a constant body weight even as our pace of life ebbs and flows. But when we eat far more than we burn, obesity results.

Weight-loss strategies typically focus on reducing the number of calories a person consumes. But this strategy doesn't work for most people, says Ronald M. Evans, an HHMI investigator at the Salk Institute for Biological Studies in La Jolla, California. "Few people can make a lifestyle change and eat less," he says.

In 2004, Evans announced he had engineered, by genetically altering the animal's muscle, a "marathon mouse" that, with no prior training, could run longer than the average mouse. Now, he is trying to create superfit mice by using drugs rather than genetic manipulation—a more practical real-world treatment. One such promising drug is already being tested in the hopes it might speed people's efforts to get in shape and help steady a fluctuating metabolism that can lead to diabetes.

Slow Twitch or Fast Twitch?

While genetic engineering "preprograms" the young muscle of his marathon mouse, Evans says, a drug faces the more daunting challenge of "reprogramming" normal adult muscle. To begin to tackle this problem, he decided to work with exploratory drugs under development by the pharmaceutical industry. Previously, Evans showed that a new class of experimental drugs can improve the ability of mice to burn fat. He reasoned that one way to improve athletic performance might be by redirecting a similar set of molecular circuits to maximize fuel consumption in muscle.

For years, Evans and his colleagues have focused on a team of proteins, known as PPARs, that call the shots in metabolism; they direct groups of genes involved in burning and storing energy. PPARgamma, for instance, prods fat cells to grab and store fat from the blood, whereas PPARdelta stokes muscles to burn fat. "One is like charging a battery and the other is like freeing up all that stored energy," says Evans.

POTENTIAL FOR ABUSE

Drugs that enhance exercise could be a boon for fighting obesity and diabetes, but they could also give athletes an unfair advantage over their competition. Like some existing doping practices—such as injecting red blood cells and taking erythropoietin (EPO), both of which increase the oxygen-carrying capacity of the blood—a PPARdelta stimulator could help athletes run, ski, or pedal farther by helping them use more oxygen. PPARdelta wouldn't alter the blood composition directly, but it would enable muscles to consume more oxygen.

"There are two concerns," says Evans. "Using the gene as the doping agent and using the drug as the doping agent." Genes injected into the tails of mice can get into cells and become active, suggesting that athletes could use the *PPARdelta* gene directly. Gene doping isn't widely practiced, but since 2003 the World Anti-Doping Agency (WADA) has included gene doping among its banned substances and practices, and Evans is working with WADA to develop a test for both the PPARdelta drug and the gene. (The International Olympic Committee founded WADA in 1999 to coordinate anti-doping efforts across all sports; many sports federations and national Olympic committees have adopted WADA's anti-doping code.)

Drugs that target PPARdelta aren't commercially available, but several pharmaceutical companies are pursuing such pills for lipid-related diseases. Once on the market, they would undoubtedly hold appeal for reprobate athletes looking for a shortcut to the winner's podium.

Because no one has tested PPARdelta drugs in human performance, Evans isn't sure how they would stack up against other doping methods. But eventually someone will make the comparisons—or even test for synergisms. Says Evans: "Lots of people ask me what would happen if you take this drug with EPO." *—R.J.D.*

Could toying with these molecules, he wondered, tip the balance of metabolism in favor of burning fat and help people lose weight? Some results produced intriguing hints of success: mice without PPARdelta grew portly when they ate a high-fat diet, whereas mice with boosted PPARdelta activity stayed slim even when they chowed down on fat.

PPARdelta is more prevalent in so-called slow-twitch muscles (the ones that power marathoners) than in fast-twitch muscles (which provide explosive power for sprinters). Slow-twitch muscles devour oxygen—an efficient way to fuel muscles without fatigue—because they are replete with mitochondria, the cellular power plants that burn fat to produce a steady stream of energy for cells. Not surprisingly, obese people tend to carry fewer slow-twitch muscle fibers than normal and are known to fatigue easily.

Evans and his team used a genetic trick to flip the PPARdelta switch to a permanently "on" position by affixing it to another gene-prodding protein; then they bred mice that produced this modified PPARdelta in muscle. As the team reported in October 2004 in *Public Library of Science (PLoS) Biology*, these animals looked like they'd done some serious distance training, even though they weren't on an exercise regime. The mice possessed an abnormally high percentage of slow-twitch fibers; they had more mitochondria and more of a protein that triggers contractions in slow-twitch muscles.

Next, the researchers subjected the animals to a stress test. They put them on a treadmill, gradually cranked up the speed, and timed how long it took the rodents to poop out. Control animals exhausted themselves in about 90 minutes, but the marathon mice with juiced-up PPARdelta scrambled for an extra hour and nearly twice the distance. They showed other signs of exercise benefit as well: they dined on a high-fat diet without gaining nearly as much weight as the control animals did, and they demonstrated increased blood flow. "Exercise causes a whole-body change, increasing metabolism, lowering blood sugar, improving response to insulin, and protecting against weight gain," says Evans. "These animals enjoy all those benefits."

More than One Way to Hustle a Mouse

OTHER FINDINGS SUPPORT the idea that genetic changes can produce high-performance animals. Harvard Medical School's Bruce M. Spiegelman, a member of HHMI's Scientific Review Board who has collaborated with Evans on other projects, generated his own team of endurance athletes as part of his studies of

PGC-1alpha and PGC-1beta. These so-called coactivator proteins link up with proteins similar to PPARs and help them turn on genes.

The PGC-1s prod cells to make more mitochondria and turn on oxygen-utilizing metabolism. Muscles forced to produce PGC-1alpha turn into slow-twitch muscles, Spiegelman's team found. They also found that turning on PGC-1beta in muscles alters muscle complement—but in a different way. Animals with PGC-1beta harbored more of an unusual, in-between muscle type: fast-twitch but, like slow-twitch, with lots of mitochondria and active oxidative metabolism.

Because these animals had a greater capacity to burn oxygen in their muscles, Spiegelman wondered if they would perform better on a treadmill. They did: PGC-1beta mice outran normal animals by 25 percent. It's not clear yet which mice to bet on—Spiegelman's rodents didn't run as long as Evans's PPARdelta mice, but Spiegelman's mice ran faster than those in Evans's experiments.

Spiegelman is investigating whether boosting PGC-1 pathways helps fight conditions in which people lose muscle, such as muscular dystrophy and muscle wasting. In addition, PGC-1s might protect against diabetes.

No Free Ride

EVANS'S GROUP HAS DELVED into a more practical way of toying with PPARdelta. In earlier studies, the animals' muscles luxuriated in activated PPARdelta their whole lives because they had been genetically altered from birth. Could the same feat be reproduced in normal mice not carrying the long-distance-running gene? Would tinkering with PPARdelta in adulthood boost performance in the absence of exercise? Evans and his team have probed these questions in new work.

Instead of altering the genome of mice, they gave the mice a drug that switches on PPARdelta. (The drug is currently being tested as a cholesterol-lowering drug in human studies.) Unexpectedly, when the researchers put the animals on the treadmill after a steady diet of the PPARdelta-activating drug, they ran no farther than normal mice. "By itself, in an adult it's not an exercise pill," concludes Evans. "Obviously, changing adult muscle with a drug is a very different undertaking than creating a permanent change in its genes."

Still, Evans remains hopeful. To better understand why the pill didn't work on its own, he and his team determined which genes cranked up in animals that took the drug and in animals that exercised. While half the genes overlapped, exercise triggered a set of genes that the pill did not. Evans thinks that, even

Studies by **RONALD EVANS** at the **SALK INSTITUTE** (top), **BRUCE SPIEGELMAN** at **HARVARD UNIVERSITY** (middle), and **GERALD SHULMAN** at **YALE UNIVERSITY** (bottom) shed light on how muscle and metabolism contribute to fitness.

Ronald Evans: Courtesy of The Salk Institute for Biological Studies Bruce Spiegelman: Jason Crow Gerald Shulman: Gale Zucker though the drug apparently missed some key elements along the way, the pill clearly shows promise.

Given the gene overlap, Evans now wonders whether the pill might *augment* exercise, if not replace it. To address this question, he and his colleagues are putting two groups of mouse runners in a head-to-head training program. One group will run several days a week at a steady but not all-out effort—the equivalent of a brisk middistance run. The other group will get the same training but will also receive the PPARdelta pill. "With the exact same training, we hope the mice with the drug will run longer," says Evans. Indeed, preliminary studies look very promising.

Even if it works, the pill shouldn't put any gyms out of business. "You can't get away with doing nothing," says Evans. "Our idea is that the pill could make exercise more beneficial by revving up metabolism." It might also give overweight people a much needed endurance boost to get through those painful first workouts.

By contrast, "a lot of the drugs being developed try to alter appetite, but it is very difficult to change appetite," Evans adds. Plus a side effect of changing appetite can sabotage the weight-loss strategy. "Your metabolism slows down during a diet, which makes it even harder to lose weight and easier to gain weight." A PPARdelta drug "does not require the willful reduction in eating," he points out, although exercise is still a must.

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Fighting Diabetes

MAKING EXERCISE EASIER might do more than just slim corpulent bodies. Faulty fat-burning pathways portend diabetes, says HHMI investigator Gerald I. Shulman at Yale University, so activating those circuits could stave off the metabolic disease. He has studied sedentary people in their 20s whose parents have diabetes. The young people aren't yet diabetic, but they're already showing insulin resistance despite having a relatively normal body mass index, and Shulman wants to understand why. His team used nuclear magnetic resonance spectroscopy to noninvasively probe the molecular basis of insulin resistance—the first sign of diabetes. They found that the muscle cells of young people with insulin resistance accumulate lipids, which in turn dampen insulin's signal, preventing cells from taking up glucose.

People with insulin resistance have 30 percent fewer mitochondria than normal, and 30 percent less capacity to metabolize lipids. They hang on to energy, says Shulman, which is useful when food is scarce but deadly in modern societies where food is abundant. Accruing lipids might prime young people for diabetes later on.

Shulman aims to prevent this fate, and exercise can help. Vigorous activity activates fatty acid oxidation in mitochondria, restores the insulin response, and boosts numbers of mitochondria. But as much as doctors prescribe physical activity, only a small percentage of patients comply, says Shulman. "If we know mechanistically what's causing diabetes, we can come up with novel agents that mimic exercise and reduce diabetes and even obesity." He's focused on altering specific biochemical pathways to prevent them from making nefarious lipids such as diacylglycerol, which Shulman posits is the main trigger of insulin resistance in liver and muscle cells.

Drugs that activate PPARdelta might help, too. Evans's group reported in the February 28, 2006, issue of the *Proceedings of the National Academy of Sciences* that fat-fed animals treated with the PPARdelta drug controlled their blood sugar better than untreated animals. Evans is now working with Salk colleague and HHMI investigator Joseph P. Noel to capture three-dimensional pictures of PPARdelta and its partner proteins to devise new and improved PPARdelta drugs. The drug they've been using is a useful lab tool, but Evans sees room for improvement. He and Noel are aiming for second-generation compounds that might, for instance, be more easily absorbed and safer or that might target specific tissues: for instance, liver for metabolic diseases in the liver, muscle for endurance, and fat for weight loss.

Such new and improved drugs won't likely permit would-be couch potatoes to avoid exercise altogether, but they might someday make people's workouts easier or more effective. ■