



GLADSTONE INSTITUTE OF CARDIOVASCULAR DISEASE NEWS

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EMBARGOED FOR RELEASE FOR APRIL 10, 2002 TO COINCIDE WITH PUBLICATION IN THE APRIL 15 ISSUE OF THE *JOURNAL OF CLINICAL INVESTIGATION*

MICE LACKING FAT-MAKING ENZYME ARE LEANER, MORE SENSITIVE TO LEPTIN AND INSULIN, GLADSTONE RESEARCHERS FIND

A modern-day Rip van Winkle, just emerging from his long sleep, might notice a difference in today's Americans. The average American is much rounder, plumper, and heavier.

Obesity has been on the rise for the past two decades. The problem has now reached epidemic proportions, with more than 50 percent of the American population now classified as overweight or obese. While government-sponsored agencies try to spread the gospel of good eating and regular exercise, more and more Americans are finding that their clothes fit tighter every day. And no effective medical therapies currently exist for people with morbid obesity.

What's the solution? Certainly not the miracle elixirs touted to melt away the pounds in a matter of weeks. The ultimate solution would be a way to stop the body from making fat. Sound like science fiction? Not to researchers at the Gladstone Institute of Cardiovascular Disease.

They've found a group of genes for an enzyme called DGAT (also called diacylglycerol acyltransferase). In animals, DGAT is essential for the last step in the production of triglycerides, the major component of fat. Mice that lack one of the DGAT enzymes, DGAT1, are leaner than mice with normal amounts of DGAT1—and twice as active—despite their high-fat diets. Put simply, without DGAT1, the mice weren't able to become obese.

Now the researchers have found a potential mechanism for this obesity resistance. They found that DGAT1-deficient mice are more sensitive to leptin, the hormone that tells the brain when the body has had enough to eat and encourages energy expenditure. They also found that these mice are more sensitive to insulin, and therefore potentially less likely to develop diabetes. The new findings are published in the April 15 issue of the *Journal of Clinical Investigation*.

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This is good news. Obese and overweight people tend to develop type 2 diabetes, or insulin-resistant diabetes, because their cells become deaf to insulin's message to store away sugars. This causes high blood sugar, a sign of diabetes, and frequently also causes high blood triglycerides.

The DGAT1-deficient mice had substantially lower tissue triglyceride levels than normal mice, and they also had lower blood sugar levels after a glucose load, indicating increased sensitivity to insulin. Moreover, they lost more weight than normal mice in response to leptin injections, indicating increased sensitivity to leptin. However, the researchers were surprised to find that DGAT1-deficient mice didn't eat less in response to being more sensitive to leptin. In fact, they ate just as much as the normal mice.

Why, then, did DGAT1-deficient mice lose more body weight than normal mice when infused with leptin? The difference most likely was that DGAT1-deficient mice responded better to leptin's message to increase energy expenditure.

"That means the mice can eat normal amounts of food and still lose weight, because they just end up burning off the calories," said Hubert C. Chen, MD, lead author of the study and research scientist at Gladstone.

The DGAT1-deficient mice also had smaller fat cells, which were less likely to enlarge when the mice ate a high-fat diet, the study found.

How can you get rid of your own DGAT1? You can't. But Chen said that a drug that inhibits DGAT1 just might be the thing to cure the obesity that ails us.

"Most human obesity is associated with resistance to leptin," Chen said. "A DGAT1 inhibitor that overcomes leptin resistance could be a potential therapy."

In fact, the researchers showed that in a strain of genetically obese mice characterized by leptin resistance, inactivation of DGAT1 significantly reduced their obesity and insulin resistance.

"Obesity is a huge public health problem, so people are looking for drugs to cure it," said Robert V. Farese, Jr., MD, senior author, Gladstone investigator, and UCSF professor of medicine. "But no one knows what kind of drug would be best." Most of the current anti-obesity drugs work on the nervous system and attempt to reduce appetite. A DGAT1 inhibitor would offer an entirely novel approach by going directly to the source and turning off the tap of fat production.

Maybe the next time Rip wakes up, a DGAT1 inhibitor will have transformed Americans into the slimmer bodies they had in the good old days.

Other authors include Steven J. Smith, PhD, postdoctoral fellow at Gladstone and the UCSF Cardiovascular Research Institute, Zuleika Ladha, research associate at Gladstone, Dalan R. Jensen, PhD, postdoctoral fellow at University of Colorado Health Science Center, Luis D. Ferreira, PhD, postdoctoral fellow at Colorado, Leslie K. Pulawa, research associate at Colorado, James G. McGuire, senior research associate at Gladstone, Robert E. Pitas, PhD, Gladstone investigator and UCSF professor of pathology, and Robert H. Eckel, MD, professor of medicine at Colorado.

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The study was funded by the National Institutes of Health, the Sandler Family Supporting Foundation, the Endocrine Fellows Foundation, the CardioFellows Foundation, and the J. David Gladstone Institutes.

The Gladstone Institute of Cardiovascular Disease is one of three research institutes that comprise The J. David Gladstone Institutes, a private nonprofit biomedical research institution affiliated with UCSF. The institute is named for a prominent real estate developer who died in 1971. His will created a testamentary trust that reflects his long-standing interest in medical education and research.

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NOTE: Researchers available for phone and in-person interviews. Please call Laura Lane at (415) 695-3833 to schedule an interview.