HarvardScience

New class of hormone from “healthy fat cells” benefits body metabolism in mice

Discovery of ‘lipokine’ signaling might eventually lead to new treatments for obesity-related conditions

September 18, 2008

Christina Roache
Harvard School of Public Health

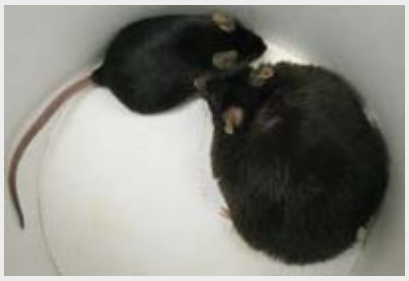

PHOTO COURTESY HARVARD SCHOOL OF PUBLIC HEALTH

A normal mouse and its grossly obese cousin.

Scientists at the Harvard School of Public Health (HSPH) have identified in mice a newly discovered class of hormones -- lipokines. In tomorrow's issue of the journal Cell they report that lipokine is a molecule in mice that helps stop, or even reverses obesity-related conditions such as insulin resistance and “fatty liver.”

Lipokines are hormones made from lipids, or fats. All other known hormones – chemical signals secreted into the blood that regulate distant cells and organs – are steroid or protein-based.

Researchers, led by HSPH Professor Gökhan Hotamisligil, knew from previous experiments that an unidentified factor in the fat tissue of genetically engineered mice sent signals to regulate metabolism in liver and muscle tissues. The researchers suspected that elucidating the mechanism could be of significance. "We initially thought the factor behind this mechanism would be a protein or a peptide hormone, and we spent a great deal of time looking for it in the wrong places," Hotamisligil said. "Then we discovered it was something sitting right in front of us -- one of the thousands of fatty acids that are released into the blood serum by fat cells."

To pinpoint the specific fatty acid, Haiming Cao, a research fellow in the Hotamisligil lab and first author of the Cell paper, used a new technology platform called “lipomics” that enables simultaneous identification of hundreds of lipids at a time. (The term “lipomics” applies to the study of lipids in a similar way to how the term “genomics” applies to the study of

genes and “proteomics” to the study of proteins). In collaboration with scientists Michelle Wiest and Steven Watkins of Lipomics Technologies, the research team painstakingly mapped all of the lipids in the bloodstream and the fat, muscle, and liver tissues of the mice suspected to have the mechanism.

After sifting through massive amounts of data, the scientists discovered the “lipokine” in the fat cells of their genetically engineered mice. The hormone, “C16:1n7”-palmitoleate, travels to the muscles and liver, where it improves cell sensitivity to insulin and blocks fat accumulation in the liver. In addition, the researchers observed that palmitoleate suppessed inflammation, which was previously identified by Hotamisligil and others to be a primary factor leading to metabolic disease.

The scientists also discovered that palmitoleate production is markedly increased in genetically manipulated animals whose fat cells lacked proteins that serve as ‘chaperones,’ or molecular carriers, for the fat absorbed from food that is deposited into fat storage cells. The lack of these proteins caused a surge in palmitoleate signaling to the muscles and the liver, where improved insulin function allowed cells to absorb nutrients more efficiently. These mice were remarkably resistant to the metabolic abnormalities that are normally associated with the long-term consumption of a high-fat diet; they did not develop diabetes, heart disease, or fatty liver.

Hotamisligil and Cao observed that these mice were unable to store much dietary fat; and in response, the fat cells actually manufactured their own fat, a process known as de novo lipogenesis. This self-made fat spurred the production of palmitoleate, leading to healthy regulation of whole-body metabolism.

“It turns out that, like most other things, the best fat is the home-made variety, the one you make yourself,” Hotamisligil said.

The scientists predicted that one effective way to utilize this discovery for therapeutic or preventive purposes would be to stimulate the production of endogenous palmitoleate by turning on the process of de novo lipogenesis. “We believe that it might be possible to chemically stimulate cells to manufacture their own 'good' fat, which could have beneficial effects on metabolism through increased palmitoleate signaling," said Hotamisligil.

The current global epidemic of obesity has spurred a sharp and worrisome increase in metabolic disorders such as diabetes and atherosclerosis, making them a leading cause of morbidity and mortality. If the palmitoleate effect in mice is found to be similarly important in humans, the effect may be tested as a potential treatment for metabolic disorders, predicted Hotamisligil. He added that palmitoleate may be found in natural products but doesn't presently exist in a pure form.

Other authors of the paper are Hotamisligil lab members Kristin Gerhold (now at the University of California in Berkeley), and Jared R. Mayers; and Michelle Wiest and Steven Watkins of Lipomics Technologies in West Sacramento, Calif.

This work was supported by a National Institutes of Health grant. Cao is supported by an NIH Roadmap Fellowship and the American Diabetes Association. Wiest and Watkins are employees of Lipomics Technologies. Hotamisligil serves as a member of the scientific advisory board at Lipomics Technologies.

HarvardScience

'Brown fat' cells hold clues for possible obesity treatments

May 26, 2005

In laboratory studies of mouse cells, the research team identified genes that govern how precursor cells give rise to mature brown fat cells. There are two main types of fat cells in the body- white, designed to store energy for use in times of need, and brown, which burn energy and generate heat, leading scientists to believe that finding ways to encourage the development of brown fat might be good for treating obesity. In previous research, the scientists were among the first to develop cell lines of precursor cells that give rise to brown fat cells. 'We used those cell lines to study how insulin affects the conversion of fat precursors, or preadipocytes, into mature brown adipocytes,' said Dr. Yu-Hua Tseng, one of the study's lead authors.

The team studied 'knockout' cell lines of brown preadipocytes that lacked insulin receptor substrates (IRS) numbered 1 through 4, which are the first steps in insulin signaling inside the cell. In cell lines lacking IRS1, the precursors failed to develop into mature brown fat cells. Importantly, when they added the gene for IRS1 back into the knockout cells, the precursors recovered most of their ability to differentiate into brown fat cells. Using DNA chips to analyze these cells, a strong genetic pattern emerged that predicted the importance of precursors to differentiate into mature brown fat cells.

Contributed by Children's Hospital

HarvardScience

Fat cells tied to whole-body insulin resistance

Molecular basis of link between obesity and diabetes has remained unclear

February 9, 2001

Research done by Barbara Kahn, professor of medicine at Beth Israel Deaconess Medical Center, and colleagues now shows that glucose uptake by fatty tissue is important for maintaining the body's ability to respond to insulin. Their results also point to a mechanism by which an abnormality in fat cells may trigger insulin resistance and ultimately diabetes. Skeletal muscle is the primary tissue for insulin-stimulated glucose uptake. Yet in obesity and Type II diabetes, expression of the primary insulin-stimulated glucose transporter, GLUT4, is normal in muscle but reduced in fatty tissue. This paradox led Kahn and colleagues to ask what role fatty tissue-expressed GLUT4 may play in the development of insulin resistance. The results clearly show that "fat is important for whole-body insulin action," said Kahn.

Contributed by Focus