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

September 18 2008

A normal mouse and its grossly obese cousin.

(PhysOrg.com) -- 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.

Provided by Harvard University