

Hormone discovery points to benefits of 'home grown' fat

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A hormone found at higher levels when the body produces its own "home grown" fat comes with considerable metabolic benefits, according to a report in the September 19th issue of the journal *Cell*, a Cell Press publication. The newly discovered signaling molecule is the first example of a lipid-based hormone—most are made up of proteins--although the researchers said they expect it will not be the last.

The findings in mice raise the paradoxical notion that treatments designed to boost the body's fat production might actually be one solution to the growing epidemic of obesity and related metabolic diseases. Likewise, diets supplemented with the fat hormone, a fatty acid known as palmitoleate, might also come with long-term benefits.

The results also reveal that, as with most things, when it comes to fat it's not fair to generalize.

"Most people think that fat is bad and the more you have the worse it is," said Gökhan Hotamisligil of Harvard School of Public Health. "To a certain extent that may be true, but it's far too simplistic. Rather than being one chemical entity, fats are actually a huge soup of things with hundreds of molecules and many different structures. In the blood, high fatty acids and triglycerides are often considered bad and low levels good, but it's not quite that way. It depends what constitutes this soup rather than how much you have."

Hotamisligil, along with study first author Haiming Cao and their

colleagues, made their discovery while studying mice that lack two specific fatty acid binding proteins (the lipid chaperones aP2 and mal1) only in their fat tissue. Those proteins bind lipids and control the fat composition of cells. Earlier studies showed that mice lacking one of those proteins become more sensitive to insulin. In addition, mice lacking both become resistant to virtually all aspects of metabolic syndrome, a cluster of obesity-associated ailments that includes diabetes, fatty liver disease, and atherosclerosis.

To further explore the animals' apparently "excellent health," the researchers measured their plasma lipid levels initially expecting to find lower than normal values. But, in fact, they found the mice to have higher circulating fatty acid levels.

"Despite those higher fatty acid levels, the animals are spectacularly healthy seemingly no matter what—even on a high fat diet," Hotamisligil said. Careful analysis of the lipids in those animals showed that their fat displayed a profile normally found in lean, insulin-sensitive mice despite consuming a high-fat diet.

Those results together with earlier studies also suggested that the changes in fat cells were having effects elsewhere in the body, specifically in the muscle and liver. They suspected it to be a protein-based hormone released by the fat, but nothing turned up.

Ultimately, they landed on the relevant actor: the fatty acid palmitoleate. They found that the normally rare fatty acid is the third most abundant free fatty acid in mice lacking those fatty acid binding proteins. In the fat tissue of normal mice, total palmitoleate concentrations drop nearly 50 percent upon exposure to a high fat diet. The mutant animals on the other hand experienced only a 10 percent decline in the fatty acid under the same conditions, evidence to explain their resistance to poor eating habits.

The fat hormone strongly stimulates insulin's effects on muscle and suppresses fat accumulation in the liver, they report. "This lipid is almost as good as insulin at pushing sugar out of the blood and it prevents fat in the liver," Hotamisligil said. "Delivering fat protects against fat, at least in the liver."

That emergence of palmitoleate in the blood is tied to changes in the activity of fat cells that occur when they convert glucose into fatty acids (a process known as de novo lipogenesis) rather than getting it from dietary sources.

"If what we postulate is correct, tricking the body to produce fat may actually be an excellent strategy for metabolic health," Hotamisligil said. Indeed, he added, there is evidence that people who are obese produce less of their own fat.

Of course, all of this assumes that the findings in mice will be applicable to humans. Hotamisligil said that it should be relatively easy to begin testing that idea by measuring palmitoleate levels in healthy people compared to those with various metabolic diseases.

Further study by his group will seek to unravel exactly how palmitoleate exerts its influence. They will also delve further into hints from the current study that the fat hormone might also have anti-inflammatory properties.

Source: Cell Press

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