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The good in fat

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Abstract

A new class of fatty acid — found in food and synthesized by mammalian tissues — enhances glucose uptake from the blood and reduces inflammation, suggesting that these fats might be used to treat diabetes.

The word fat has an almost universally negative connotation in modern society, whether as a pejorative term for describing someone who is overweight or as a foodstuff reviled for its deleterious impact on health. Obesity is associated with elevated levels of multiple kinds of fat, and fat accumulation in tissues is thought to contribute to the development of the unholy trinity of disorders that characterize type 2 diabetes: failure to respond to the glucose-regulating hormone insulin; failure to control glucose production by the liver; and failure of pancreatic β -cells, which store and release insulin. Now, however, Yore *et al.*¹ report in *Cell* that certain modified fatty acids are found at low, rather than elevated, levels in obese, insulin-resistant humans and mice. Furthermore, they show that administering these fatty acids to such mice improves glucose uptake from the blood, enhances insulin secretion and relieves obesity-associated inflammation, suggesting that these naturally occurring fats could be used for diabetes therapy.

Fatty acids and closely related glycerolipid molecules wear multiple biological hats, serving as a major energy reservoir, as constituents of cell membranes and as mediators of intracellular signalling. Yore and colleagues' report adds to emerging evidence implicating specific, low-abundance fatty acids as hormone-like 'lipokine' molecules involved in metabolic regulation.

The same research group had previously shown² that elimination of the glucose-transport protein GLUT-4 from adipose (fat-storing) tissue resulted in insulin resistance in liver and muscle — a condition in which cells of these organs have an impaired capacity to increase glucose uptake in response to insulin, contributing to the abnormally high blood-glucose levels that define diabetes. By contrast, adipose-specific overexpression of GLUT-4 caused higher glucose uptake than in control mice — making the mice more sensitive to insulin despite also increasing fat synthesis and levels of circulating fatty acids³.

The lipid-generating impact of GLUT-4 overexpression was predictable, given that fat cells (adipocytes) use glucose for fat synthesis. But surprisingly, the enhanced glucose uptake was eliminated by adipose-specific deletion of the transcription factor ChREBP, which regulates fat synthesis, suggesting that the glucose-uptake effect depended on lipo-genesis⁴. This finding led Yore and colleagues to the hypothesis that certain fatty acids have positive effects on glucose regulation.

The authors used mass spectrometry to compare the lipid content of the blood serum and adipose tissue taken from these 'diabetes-resistant' mice to that of normal mice. They identified five lipids that were significantly elevated in the modified mice, four of which were made up of a typical long-chain fatty acid (palmitate, oleate, stearate or palmitoleate) joined by an ester bond to a hydroxylated version of one of the same set of fatty acids. The authors refer to these compounds, which had not been described previously, as fatty-acid esters of hydroxyl fatty acids (FAHFAs).

Interestingly, only 6 of the possible 16 FAHFA species were upregulated by GLUT-4 overexpression. The most dramatically upregulated type of FAHFA in the GLUT-4-overexpressing mice was palmitic acid hydroxystearic acid (PAHSA), which was then studied further. Yore *et al.* report that PAHSA (which exists in several isomeric forms depending on the esterification position) can be synthesized by mice provided with the hydroxylated fatty-acid precursors, and that it and other FAHFAs are present in mouse serum at low nanomolar concentrations and in laboratory-mouse and human food (Fig.1). Surprisingly, the levels of FAHFAs are much higher in low-fat, 'standard' mouse diets than in high-fat mouse diets used to induce obesity and insulin resistance. These findings suggest that both dietary intake and endogenous synthesis can influence tissue and blood concentrations of FAHFAs.

The authors then studied these fatty acids in two models of insulin resistance in mice: fasting and high-fat feeding. Although they found that PAHSA levels fluctuate in response to nutritional state, the direction and magnitude of the changes depended on the PAHSA isoform analysed and the tissue in which they were measured, suggesting that PAHSA abundance in various tissues is not clearly correlated with insulin sensitivity in these rodent models. However, in humans, they observed a strong association between PAHSA and insulin sensitivity, and PAHSA levels were significantly lower in insulin-resistant than in insulin-sensitive individuals.

To test the functional significance of PAHSA in glucose regulation, the authors administered the fatty acid orally to mice before performing a glucose-tolerance test, which measures how quickly a dose of glucose is cleared from the blood. They observed reduced basal glucose levels and more-efficient glucose clearance than in mice that had not received PAHSA, and suggested that this effect might be due to improved insulin sensitivity. Although they did not test this idea in mice, they observed a modest potentiation of insulin-stimulated glucose uptake in adipocytes *in vitro* following the addition of PAHSA. However, PAHSA administration to mice also caused increased levels of insulin and glucagon-like peptide-1 (a gut hormone that enhances insulin secretion) in the serum, which might also explain the improved glucose uptake (Fig. 1). Thus, the mechanism by which PAHSA lowers blood glucose remains to be defined.

FAHFAs are not the only lipids for which therapeutic roles have been suggested in diabetes and related metabolic disorders. For example, administration of a monomeric fatty acid, palmitoleate, which is also produced in adipose tissue during periods of increased fat synthesis, decreases the liver fat content of mice and enhances insulin sensitivity in their skeletal muscles⁵. However, the strong associations between PAHSA and human insulin resistance demonstrated by Yore *et al.* have not been seen for palmitoleate. Omega-3 fatty acids have been suggested to protect against metabolic diseases by stimulation of the G-protein-coupled receptor GPR120, resulting in reduced inflammation, improved insulin sensitivity and translocation of GLUT-4 from the cell interior to the cell surface⁶. Yore *et al.* demonstrate that PAHSA also decreases the production of the proinflammatory molecules IL-1 β and TNF- α by macrophage cells, and that both this effect and PAHSA-induced enhancement of glucose uptake and GLUT-4 translocation are prevented by inhibiting the activity of GPR120 (Fig. 1). Thus, it seems that FAHFAs and omega-3 fatty acids may converge, at least in part, on the same receptor system to regulate glucose uptake and inflammation. It will be interesting for future studies to compare which is the more potent and efficacious lipid in this regard.

It remains to be determined how the different actions of FAHFAs — sensitizing cells to insulin, stimulating insulin production and reducing inflammation — contribute to glucose homeostasis. Other questions worthy of future investigation include which enzymes are involved in synthesizing and degrading FAHFAs and how they are regulated by changes in diet or, perhaps, by the composition of microorganisms in the gut. Finally, and importantly, the effects of FAHFA administration on glucose control in humans with type 2 diabetes remains to be explored. Results of these studies will determine whether FAHFAs or their derivatives may indeed become therapeutic agents for metabolic diseases.

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Figure 1. Anti-diabetic and anti-inflammatory effects of fatty acids

a, Yore *et al.*¹ describe a new class of fatty acid, called fatty-acid esters of hydroxyl fatty acids (FAHFAs), that are present in foods and that can be produced by adipocytes from newly synthesized long-chain fatty acids that are joined by esterification to hydroxylated fatty acids. Lipogenesis, the process of converting glucose to new fats, is catalysed by the enzyme FAS and activated by ChREBP, a glucose-responsive transcription factor. **b**, The authors show that administering FAHFAs to mice results in more-efficient clearance of glucose from the blood and suggest that this occurs through increasing secretion of, and sensitivity to, insulin, a hormone secreted by pancreatic β -cells. In adipocytes *in vitro*, FAHFAs activate the receptor GPR120, which increases translocation of the glucose receptor GLUT-4, and thereby enhances insulin-stimulated glucose uptake. Administration of FAHFAs *in vivo* leads to increased serum levels of insulin and glucagon-like peptide-1 (GLP-1), a gut hormone that enhances insulin secretion. In addition to these anti-diabetic

effects, FAHFA activation of GPR120 reduces the production of the inflammatory molecules IL-1 β and TNF- α by macrophage cells of the immune system.

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