Lots of Fat, No Carbs--And the Right Hormone

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Crisco inferno. Liver from fasting mice without FGF21 (left) fills with fat, whereas those with the hormone (right) burn it up. (Kliewer lab)

Whether a high-fat, low-carbohydrate diet melts your kilos away may hinge on your propensity to produce a single hormone—no matter how diligently you stick with the cheese. Two studies published in the June issue of Cell Metabolism clarify how a protein regulates fat burning when the body switches from carbohydrates to fat reserves for energy. The findings could one day help people struggling with type 2 diabetes, obesity, or other metabolism disorders.

When the body is fed lots of fat and few carbohydrates—an Atkins diet without the protein—it gears into starvation mode. Without an easily digestible dose of sugar and starch, the body taps its fat stores, shipping fat molecules from the adipose tissue to the liver, where they’re broken down into ketones (which is why researchers call it a ketogenic diet). Eleftheria Maratos-Flier, an endocrinologist at Beth Israel Deaconess Medical Center in Boston, wondered what triggered the change.

She and her colleagues fed mice either a ketogenic or a regular diet for 30 days. Liver levels of FGF21, a protein with a known role in metabolism, jumped in mice fed a ketogenic diet, then plunged once they ate a regular meal. Intrigued, the researchers engineered transgenic mice that could not make enough of the hormone and fed them the same diet. "Their liver blew up with fat," says Maratos-Flier. Without the ability to burn triglycerides, cholesterol, or free fatty acids, the result was "mouse foie gras," she quips. This shows that the body relies on the hormone in switching to breaking down fat.

The hormone flicks a switch in behavior, too. In a separate study, Steven Kliewer, a molecular biologist at the University of Texas Southwestern Medical Center in Dallas, and colleagues fed normal mice and transgenic mice that overproduce the hormone a regular diet, then starved them for a day. Normal mice didn’t change their habits. But body temperature of transgenic mice plummeted and they stopped moving, entering into a hibernation-like state called torpor. "All of this was completely unexpected," he says. "They looked like they were starved, even when they were fed."

The hormone’s knack for revving up fat metabolism and weight loss, added to earlier evidence that it makes blood sugar levels drop, may lead to treatments for people with type 2 diabetes or obesity, Kliewer says. Maratos-Flier’s lab hopes to explore whether obese mice given the hormone will get lean again.

Studies like these two will eventually help tailor diets to people based on their physiology and genes, says obesity researcher Randy Seeley of the University of Cincinnati, Ohio. But he cautions that mouse and human livers aren’t the same; what’s more, whereas Atkins-like diets seem to work in humans because they eat less, mice lose the weight through exercise. That makes him skeptical that the studies will apply directly to humans.