Study identifies new regulator of fat metabolism

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Over the past several years, animal studies have shown that high-fat, low-carbohydrate “ketogenic” diets cause demonstrable changes in metabolism and subsequent weight loss. Now, researchers at Beth Israel Deaconess Medical Center (BIDMC) have identified a key mechanism behind this turn of events. Their findings, which appear in the June 2007 issue of Cell Metabolism, demonstrate that a liver hormone known as FGF21 is required to oxidize fatty acids – and thereby burn calories.

"When the diet is extremely low in starches and sugars, blood sugar levels drop substantially so that muscle and brain have to turn to alternative fuels,” explains senior author Eleftheria Maratos-Flier, MD, an investigator in the Department of Endocrinology, Diabetes and Metabolism at BIDMC and Associate Professor of Medicine at Harvard Medical School. “Consequently, fatty acids are broken down in the liver and converted to ketones, which then serve as a major fuel source.”

Known as ketosis, this metabolic state is characterized by extremely low insulin levels, as would occur during periods of fasting or starvation or while consuming a low-carb diet, such as the popular Atkins diet model.

For the past several years, Maratos-Flier’s laboratory has been studying the physiologic states of animals consuming various types of diets -- including standard “animal chow” diets and diets moderately high in both fats and carbohydrates, as well as ketogenic diets. And she has found through her experiments that even though mice are fed exactly the same number of calories, the composition of the calories causes them to gain

weight in different ways.

“The differences in weight gain reflect differences in metabolic rates,” she explains. “These, in turn, result in hormonal changes that lead to different disposition of the calories.”

In this latest paper, Maratos-Flier and colleagues studied mice that had been fed a ketogenic diet high in both saturated fat and unsaturated fat and practically devoid of carbohydrates.

“Despite the high fat content of this diet, the study animals maintained normal levels of circulating lipids,” she explains. “We wanted to learn what factors might be responsible for creating this state in which consumed calories were being burned off in the liver rather than being stored as fat.”

Because the physiologic changes in the animals didn’t appear to be explained by typical hormonal regulators – neurotransmitters that normally regulate appetite -- the researchers set out to identify which genes were unique to this ketogenic phenotype, exploring the possibility that hepatocytes were playing an active role in the process.

And, using micoarray gene analysis, they discovered that their hunch was correct: FGF21, a liver-derived fibroblast growth factor gene, was significantly increased in the mice that had been fed ketogenic diets.

“FGF21 had previously been identified as a potential metabolic regulator by scientists at Eli Lilly, who showed that transgenic mice that overexpressed FGF21 were protected from diet-induced obesity, had smaller fat cells and had more brown adipose tissue,”says Maratos-Flier. “But little was actually known about FGF21’s physiologic roles. Working with Jeffrey Flier’s lab, we were able to show that FGF21 is essential for fatty acid oxidation.”

Furthermore, she explains, when FGF21 was inhibited, the mice developed a massive accumulation of fat in the liver and an extreme increase in circulating lipids.

A second study by Maratos-Flier and colleagues published in the June 2007 issue of the American Journal of Physiology further elucidates the unique metabolic changes that occur with the consumption of a ketogenic diet.

“Although the purpose of both of these studies was to glean insights into metabolic physiology, our findings suggest that increased levels of FGF21 may be a potential mechanism behind low-carbohydrate diets’ beneficial properties when it comes to lipid metabolism,” says Maratos-Flier. “Diets that limit carbohydrates and eliminate transfats, and at the same time emphasize fiber and good fats, appear to be healthiest, especially among individuals who are predisposed to developing diabetes.”

Source: Beth Israel Deaconess Medical Center