Scientists discover new clues to how weight loss is regulated

October 23 2014

A hormone seen as a popular target to develop weight-loss drugs works by directly targeting the brain and triggering previously unknown activity in the nervous system, UT Southwestern Medical Center obesity researchers have found.

The fibroblast growth factor 21 (FGF21) hormone has been a key target for developing weight-loss drugs because the protein increases energy expenditure, causing the body to burn calories. But how the hormone worked wasn't known until now.

UT Southwestern researchers tracking the hormone discovered that FGF21 acts directly on the brain, activating another hormone called corticotropin-releasing factor (CRF). CRF then stimulates the nervous system, activating brown adipose tissue, which generates body heat by burning fat.

"FGF21 is well known for playing a role in weight loss and we had previously shown that the hormone can act directly on the brain in mice to influence functions like reproduction. In the new study we show that FGF21 also acts directly on the brain to regulate obesity," said Dr. Steven Kliewer, Professor of Molecular Biology and Pharmacology, who holds the Nancy B. and Jake L. Hamon Distinguished Chair in Basic Cancer Research at UT Southwestern.

Specifically, researchers found that the FGF21-CRF pathway activates a part of the nervous system that controls various involuntary body

functions, called the sympathetic nervous system, to signal to brown fat. Brown fat is often considered the "good" fat that actually burns energy by generating heat—called thermogenesis—to protect from the cold. Once brown fat receives a "weight loss" signal, the tissue burns fat.

The findings, published in the journal *Cell Metabolism*, are important to ongoing efforts to understand obesity at a molecular level and thus better respond to the obesity epidemic.

More than one-third of U.S. adults—about 35 percent—are obese, according to the Centers for Disease Control, with obesity-related conditions such as heart disease, stroke, type 2 diabetes, and certain types of cancer among the leading causes of preventable disease. Obesity also takes a dramatic financial toll, costing an estimated $150 billion annually or, on an individual basis, an additional $1,429 in higher medical costs than those of normal weight.

"We have made great strides in understanding obesity in recent years," said senior author Dr. David Mangelsdorf, Chairman of Pharmacology, a Howard Hughes Medical Institute investigator, and holder of the Distinguished Chair in Pharmacology, and the Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology in Honor of Harold B. Crasilneck, Ph.D. "What this research shows is that the central nervous system must be considered when looking for weight loss treatments."

Dr. Mangelsdorf and Dr. Kliewer are members of UT Southwestern's Taskforce for Obesity Research (TORS), composed of investigators from diverse disciplines who examine the behavioral, metabolic, and cellular mechanisms that cause obesity and metabolic syndrome. Their primary goal is to elucidate how the brain regulates food intake and energy expenditure, and to determine how dysregulation of glucose and lipid metabolism in the liver causes the metabolic syndrome. The long-

term goal is to develop more directed approaches to prevent obesity and treat related metabolic complications. Dr. Mangelsdorf and Dr. Kliewer are part of the team studying the molecular biology of energy metabolism.

Provided by UT Southwestern Medical Center