Einstein researchers have found a molecular explanation for the hunger pangs caused by lack of food. Their discovery could lead to an entirely new way to treat obesity and the type 2 diabetes that often results from it.

Scientists have long known that starvation activates a process called autophagy, in which cells cannibalize some of their own components to survive. Autophagy also provides an “important cellular recycling mechanism” that allows cells to digest organelles and damaged proteins they no longer need, says Rajat Singh, M.D., M.B.B.S. (right), an assistant professor of medicine (endocrinology) and of molecular pharmacology.

But autophagy does more than recycle cellular trash for energy. As a postdoctoral fellow working with Einstein’s Mark J. Czaja, M.D., and Ana Maria Cuervo, M.D., Ph.D., Dr. Singh found that autophagy helps to degrade fat in the liver.

“We were looking at fat deposits in hepatocytes—liver cells—which is often a complication of diabetes,” says Dr. Singh. In a 2009 study published in Nature, Dr. Singh and colleagues showed...
An On/Off Switch for Hunger (continued)

that inhibiting autophagy in mice caused their liver cells to accumulate fat—clear evidence that autophagy does indeed control fat levels in the liver. “We actually observed a vicious cycle,” says Dr. Singh, “in which decreased autophagy causes livers to become fatty—and this accumulating fat makes things worse by further suppressing autophagy.”

But Dr. Singh and his colleagues found that elsewhere in the abdomen—in fat tissue—autophagy actually helps to form fat tissue. When the researchers shut down autophagy in fat tissue, mice remained lean and protected against diabetes despite being fed a high-fat diet, since they now burned fat instead of storing it.

A Switch in the Brain

“These results were so exciting that we started thinking about what else autophagy might be doing,” says Dr. Singh. So he decided to look at the brain—more specifically, at a specialized set of brain cells (hypothalamic neurons) that regulate how much animals eat by monitoring their nutrient intake.

Sure enough, Dr. Singh (now in charge of his own lab at Einstein) found that autophagy also occurred in these crucially important neurons. More specifically, when starvation switches on autophagy in these neurons, small fat droplets within the neurons are digested; this produces free fatty acids, which boost levels of a neuronal molecule that prompts the animal to begin feeding.

The next step was for Dr. Singh to use genetic engineering techniques to shut down autophagy in those “hunger neurons” of the brain. The result? Mice whose neurons could not activate autophagy following an overnight fast ate less than mice in which autophagy remained intact. Those important findings were published last year in Cell Metabolism, with follow-up work published in EMBO Reports this year.

“If we can identify the appropriate molecular targets and find the right drugs, we might be able to manipulate autophagy in an organ-specific manner to control obesity,” says Dr. Singh. Promoting autophagy in the liver, he notes, could burn fat and prevent it from accumulating. By contrast, shutting it down elsewhere—in fat tissue and in nutrient-sensing neurons in the brain—could help curb appetite and keep us lean and healthy.

ON THE WEB

To learn more about the Diabetes Research Center, please visit www.einstein.yu.edu/diabetes

Q: How does losing weight fight diabetes?

A: For overweight people with type 2 diabetes, losing 10 to 15 percent of total body weight can help lower blood sugar (glucose). That’s because being overweight causes a condition called insulin resistance, in which insulin that people produce—needed for moving glucose from the bloodstream and into cells—isn’t efficiently used by their bodies. So sugar levels in the blood become elevated, leading to type 2 diabetes.

For people who have type 2 diabetes, losing weight can help reverse insulin resistance: Their cells become more sensitive to insulin, allowing them to use insulin more efficiently. As a result, people with type 2 diabetes may be able to reduce—or even eliminate—the drugs they’re taking to normalize their blood sugar levels.
Hospitals and Hypoglycemia

Laura Boucai, M.D., M.S.
Assistant Professor of Medicine
(Endocrinology)
Albert Einstein College of Medicine
Attending Physician, Endocrinology
Montefiore Medical Center

About one in every 10 hospitalized patients experiences hypoglycemia, or abnormally low blood glucose levels. Some are cases of “drug-associated hypoglycemia”—the result of hospitals’ aggressive efforts to control patients’ hyperglycemia (high blood sugar), a risk factor for increased morbidity and mortality. But could hospital-induced hypoglycemia also be jeopardizing patients’ health?

In a large study published in 2011 in the American Journal of Medicine, Dr. Boucai and colleagues looked at hypoglycemia cases among patients admitted to the general wards of Montefiore, the University Hospital and academic medical center for Einstein. Drug-associated hypoglycemia was not linked to increased mortality risk. Instead, such a link existed only among patients who developed hypoglycemia spontaneously. This spontaneous hypoglycemia, the researchers concluded, may not directly cause death but instead may be a “marker” of serious illness. The researchers note that these findings “should reassure clinicians who manage glucose levels in hospitalized patients in the general wards.”

Quick Course: Prediabetes

In prediabetes, someone’s blood glucose or A1C (glycosylated hemoglobin) level—a measure of blood sugar levels over the previous three months—is higher than normal but not high enough to be classified as diabetes. In 2005–2008, 35 percent of U.S. adults age 20 or older had prediabetes, according to the Centers for Disease Control. This condition increases the risk for type 2 diabetes and also for heart disease and stroke. Fortunately, people with prediabetes who lose weight and increase physical activity can prevent or delay type 2 diabetes and in some cases return blood glucose levels to normal.

<table>
<thead>
<tr>
<th>A1C</th>
<th>5.7 percent to 6.5 percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>100 mg/dl to 126 mg/dl</td>
</tr>
<tr>
<td>Oral glucose tolerance test</td>
<td>140 mg/dl to 200 mg/dl</td>
</tr>
</tbody>
</table>

Source: American Diabetes Association
Congratulations!

Meredith A. Hawkins, M.D., professor of medicine (endocrinology), director of Einstein’s Global Diabetes Initiative and attending physician in the division of endocrinology at Montefiore, received an Outstanding Investigator Award from the American Federation for Medical Research in April. Dr. Hawkins was selected for her work on the liver’s role in glucose regulation and production, and how elevated fatty acids contribute to insulin resistance and inflammation.

Einstein Overseer Diane Belfer has made a generous commitment to establish the Diane Belfer, Cypres & Endelson Families Faculty Scholar in Diabetes Research at the College of Medicine. Teresa P. DiLorenzo, Ph.D., professor of microbiology & immunology and of medicine (endocrinology), will be the first faculty member to hold the newly created academic position.

Dr. DiLorenzo’s research focuses on type 1 diabetes, an autoimmune disease caused when T cells of the immune system destroy the insulin-producing beta cells in the pancreas. Her laboratory has identified a protein called IGRP that juts from the surface of beta cells and that T cells appear to target. Dr. DiLorenzo and her colleagues are exploring strategies to short-circuit the attraction between T cells and proteins such as IGRP, as well as ways to manipulate T cells to make them tolerate such beta-cell proteins rather than attack them. These strategies may lead to therapies that can halt the progression of early diabetes or prevent the disease entirely.

A longtime leading supporter and a Benefactor of the College of Medicine, Diane Belfer has served on the Board of Overseers since 1989. “We are extremely grateful to Diane Belfer and her children for establishing this important new academic position at the College of Medicine,” says Allen M. Spiegel, M.D., Einstein’s Marilyn and Stanley M. Katz Dean, who is a noted endocrinologist and former head of the National Institute of Diabetes and Digestive and Kidney Diseases. “Mrs. Belfer’s vision and generosity will play a significant role in helping advance potentially groundbreaking work in the field of diabetes research.”

NOTABLE GIFTS

The Albert Einstein Diabetes Research Center (DRC) gratefully acknowledges the generosity of the individuals and organizations whose support is critical to advancing its mission.

DRC Hosts Meeting

In May, it was our turn to host the New York City Regional Diabetes Meeting, which brought experts from Mount Sinai, the University of Pennsylvania, Columbia University and Weill-Cornell Medical Center to Einstein for a day of information exchange. Einstein presenters were Derek M. Huffman, Ph.D. (IGF-1 paradox of aging), Clemence Blouet, Ph.D. (role of forebrain-hindbrain nutrient-sensing circuits in energy homeostasis) and Rajat Singh, M.D., M.B.B.S. (autophagy in cellular energy balance).

To learn more about supporting the work of the DRC, please contact:

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Diabetes Research Center

Our mission:
- To support and conduct basic and clinical research related to diabetes and its causes, treatment and complications
- To encourage research that will rapidly lead to diabetes therapies, especially in minority and underserved populations

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