Mice reveal another genetic clue to obesity

Just before proteins roll off a cell's assembly line, a crew of enzymes buffs, polishes, and trims them, prepping them for the jobs ahead. For many proteins, especially hormones such as insulin, a crucial enzyme called carboxypeptidase E (CPE) marks the end of the assembly line. It snips off a few final amino acids, rendering biologically inactive proteins active.

But if CPE calls in sick, the final products fail to meet manufacturer's standards. At least in mice, that may have unfortunate consequences. Researchers have identified a defective CPE gene as the reason mice belonging to a strain known as "fat" slowly grow obese and become susceptible to diabetes.

This result, reported in the June NATURE GENETICS, adds the CPE gene to a growing list of obesity-related genes that have been uncovered in mice within the last few years. Late last year, for example, researchers found the gene for a protein that apparently tells the body when it's sated (SN: 12/3/94, p.372).

Though it remains unclear how CPE defects cause obesity and how big a role the enzyme may play in human obesity, the new findings intrigue researchers. Fat mice match the progression of obesity in humans more closely than do other naturally obese strains of mice, which are often overweight almost from birth.

"These mice seem much more representative of the garden variety obesity that matures with old age," says Edward H. Leiter of the Jackson Laboratory in Bar Harbor, Maine. Leiter and his colleague Jürgen K. Naggert head the collaboration that investigated the fat mice; it also includes researchers from Albert Einstein College of Medicine in New York and the University of Chicago.

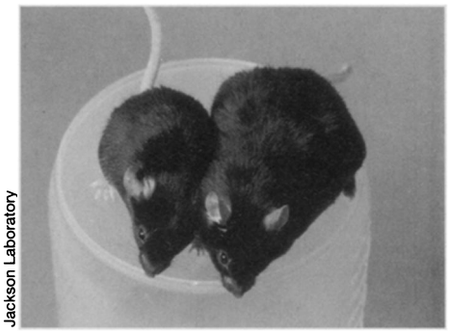
The connection between CPE and the fat strain came unexpectedly. Leiter had injected two fat mice with insulin, the hormone that controls the amount of glucose in the blood. Leiter expected no reaction, because he and other researchers thought fat mice were insulin-resistant; after all, the animals often develop diabetes despite apparently high concentrations of insulin in their blood.

To Leiter's surprise, however, blood sugar in the two mice dropped precipitously. "We had to rescue them with glucose injections," he says.

When Leiter and his colleagues analyzed the mice more closely, their bewilderment lifted. The fat mice were in fact low on insulin; previous assays had confused insulin with proinsulin, a precursor molecule from which insulin is made. More than 75 percent of a fat mouse's "insulin" is actually proinsulin, they report.

By looking at known genetic markers after a series of breeding experiments with the fat mice, Leiter and Naggert's group established that the mutated gene responsible for the strain lies right at the known location of the CPE gene on chromosome 8. "We're fairly certain they're one and the same," says Leiter.

Bolstering their case, he and his colleagues found a 20-fold reduction of CPE enzyme activity in the pancreas and pituitary of fat mice. They also showed that the CPE gene in fat mice produces a slightly flawed version of the enzyme.



Jackson Laboratory

The hefty mouse on the right has a defective gene for an enzyme that processes insulin and other proteins.

Researchers propose that this mutant form is unstable and cannot perform CPE's duties—notably, the conversion of proinsulin and other hormone precursors to their final forms.

"They present a very clear, cogent argument. I think they've got it," says David B. West of Louisiana State University in Baton Rouge, who studies animal models of obesity.

A crucial unanswered question is how CPE's absence promotes obesity in fat mice. Researchers think it results not from a failure to convert proinsulin to insulin, but rather from an inability to transform one or more of the other proteins upon which CPE acts.

Another important issue is whether and how often the problems of fat mice pop up in humans. "It will be relatively easy to see if there are CPE defects in humans," predicts West. Indeed, Naggert says that a California biotechnology company has already started surveying a large population of obese people for problems with the enzyme. *—J. Travis*

Additional source of dietary 'estrogens'

Many canned foods on supermarket shelves contain small quantities of an estrogenlike pollutant, a new study reports. This hormone-mimicking contaminant—bisphenol-A (BPA)—appears to leach from the plastic resins coating the inside of affected cans.

Exposure to estrogen mimics has become a source of growing concern since recent studies began linking these ubiquitous contaminants with increased risks of breast cancer (SN: 7/3/93, p.10) and reproductive abnormalities (SN: 1/22/94, p.56). During the past 4 years, endocrinologists have identified two types of plastics that can shed estrogen-like constituents.

Realizing that many food processors coat cans to avoid flavor-altering chemical reactions between the cans and their contents, Nicolás Olea and his coworkers at the University of Granada in Spain analyzed 20 different brands of canned goods. Purchased locally and in the United States, these included corn, artichoke hearts, mushrooms, tomatoes, and peas.

BPA turned up in roughly half of the items, the researchers report in the June ENVIRONMENTAL HEALTH PERSPECTIVES. Food processors note that about 40 percent of food cans in Spain are lined with plastic, compared to 85 percent in the United States.

Two years ago, David Feldman and Aruna V. Krishnan of Stanford University School of Medicine reported that BPA can leach from plastic subjected to high temperatures, such as those that occur during the autoclaving of laboratory equipment (SN: 7/3/93, p.10). Olea told SCIENCE NEWS that the sterilization of canned foods closely resembles that process.

Once plastic has been heated, BPA can continue to leach out. For instance, when a plastic-lined can was washed out and refilled with water, that water soon picked up measurable quantities of BPA, Olea's team reports. The pH of the food did not appear to affect leaching.

Where present, BPA occurred in trace quantities—just 4 to 22 micrograms per 300 grams of food. That's well below the 3 milligrams per kilogram of BPA allowed under regulations set by the European Union. BPA is also FDA-approved, and "no research or experience has suggested it might cause any adverse effects," says Roger Coleman of the National Food Processors Association in Washington, D.C.

Feldman's studies indicate that BPA possesses only one-thousandth the potency of estradiol, the major estrogen in humans. However, the body breaks down estradiol quickly, notes endocrinologist Ana M. Soto of Tufts University School of Medicine in Boston. If BPA lasts longer than estradiol or if the body cannot inactivate BPA as efficiently, "then it might prove more active than it at first sight appeared," she says.

—J. Raloff