Obesity researchers feast on two scoops

Obesity researchers rang in the New Year with two significant developments. One team of investigators reported finding a protein on cell surfaces that binds to leptin, a recently discovered hormone secreted by fat cells. A second team showed that a small protein, when infused into the brains of ravenous rats, dramatically stifles the rodents' appetites.

The discovery of a cellular receptor for leptin marks a milestone in the intense search that began when investigators found the mutated gene responsible for a strain of obese mice (SN: 12/3/94, p. 372). The gene, named *ob*, contains instructions for making leptin.

Obesity researchers generally agree that leptin regulates body weight by telling the brain how much fat is stored. But since the hormone's discovery, investigators have debated whether leptin itself can provide a therapeutic option for physicians treating obesity.

Injections of leptin cause normal mice to lose weight and prevent the obesity that would otherwise develop in mice with flawed *ob* genes (SN: 7/29/95, p. 68).

Other research, however, has shown that obese humans generally have higher than normal concentrations of leptin in their blood, suggesting that for most of them the problem may be a failure of the brain to respond to leptin's signal. That hypothesis prompted a vigorous hunt for leptin receptors.

Investigators from Millennium Pharmaceuticals in Cambridge, Mass., and Hoffmann–La Roche in Nutley, N. J., announced success in the Dec. 29, 1995 CELL.

"This is a fundamentally important step, finding the first receptor for a new hormone," says Timothy J. Rink of Amylin Pharmaceuticals in San Diego. "I'm sure a lot of people will turn their attention away from *ob* to this receptor."

To discover the novel receptor, the investigators surveyed a number of mouse cell types and tissues to determine which ones would bind molecules of leptin. They discovered that a brain-enveloping membrane known as the choroid plexus seemed to soak up leptin.

The choroid plexus filters the molecules allowed into the brain, and it also secretes the cerebrospinal fluid that fills the brain and spinal cord. "It's one of the guardians of the blood-brain barrier," says Louis A. Tartaglia of Millennium.

Tartaglia and his colleagues examined the many proteins made by the cells of the choroid plexus until they found the one to which leptin was binding. They then determined the DNA sequence of the genes that encode the mouse and human forms of this receptor.

The chromosomal location of the mouse gene supports the contention that it codes for a key leptin receptor, says Tartaglia. About 30 years ago, researchers discovered a strain of mice whose abnormalities, which include obesity and diabetes, are identical to those of mice with flawed *ob* genes. At the time, researchers proposed that the genetic mutation responsible for the second strain disrupts the brain's response to *ob*'s product, now known as leptin, perhaps by altering a receptor.

Over the years, investigators narrowed the location of this other mutant gene, called *db*, to a small region on mouse chromosome 4, but the gene has not yet been identified. The gene for the newly discovered leptin receptor "maps to the same one three-hundredth of the genome," notes Tartaglia. Investigators plan to examine whether mutations in the receptor gene occur in *db* mice.

The relationship between the leptin receptor and the hormone's role in regulating fat remains unclear. While many types of brain cells display the receptor, so do other tissues such as the kidneys and the lungs. Furthermore, the abundance in the choroid plexus may mean that the receptor merely helps leptin enter or leave the brain.

Nevertheless, says Tartaglia, the leptin receptor "certainly has the potential to be an important drug target." With the receptor in hand, investigators can now more easily design or screen for compounds that bind to it.

The second advance in obesity research comes from Stephen R. Bloom of Hammersmith Hospital in London and his colleagues. A few years ago, Bloom's group showed that receptors for a protein called glucagonlike peptide 1 (GLP-1) exist in the hypothalamus, a brain region crucial to the regulation of feeding.

In their recent experiments, reported in the Jan. 4 NATURE, Bloom and his colleagues injected GLP-1 into the brains of rats that had fasted. When the investigators made food available, those rats ate only 5 percent as much as untreated rats that had fasted. GLP-1 acts as "a powerful inhibitor of feeding," says Bloom.

The investigators also injected into other satiated rats a compound that blocks GLP-1 from attaching to its receptor. Those rats ate twice as much as untreated satiated rats did.

The British group suggests that GLP-1, currently under development as an antidiabetic drug, may play a crucial role in the leptin signaling pathway. "The effects of leptin *could* work entirely through GLP-1," speculates Bloom. His group proposes that drugs that mimic or block GLP-1's actions might offer effective treatments for a variety of appetite disorders. — *J. Travis*

Government guidelines okay vegetarian diet

Vegetarians take heart: The federal government finds that meatless diets can satisfy the requirements of its newly updated "Dietary Guidelines for Americans."

This week, officials of the Department of Agriculture (USDA) and the Department of Health and Human Services (HHS) tacitly endorsed vegetarian diets in the guidelines for the first time. They also emphasized the importance of exercise in combination with a healthful diet in maintaining weight, and they eliminated any allowance for middle-aged spread.

"These guidelines are the gold standard for nutrition and health," says HHS Secretary Donna E. Shalala. She notes that because 300,000 people in the United States die each year as a result of poor diet, "we are sending the message loud and clear: Diet and exercise are twin engines that will carry you on the road to a longer, healthier life."

Every 5 years since 1980, the two agencies have created and published guidelines based on the recommendations of an advisory committee. The 1995 update, released Jan. 2, still relies on the food pyramid that instructs people to base their diets on breads and cereals, fruits, and vegetables and to limit fats, salt, and sweets. It also suggests that people restrict daily fat intake to no more than 30 percent of their daily calories.

The guidelines now confirm that vegetarian diets can satisfy those requirements. However, they also note that vegetarians should be sure to get enough zinc, iron, and B vitamins, either in their diets or via supplements.

The guidelines emphasize that adults should not allow their weight to creep up with age, and they advise that adults get 30 minutes of moderate exercise such as gardening, housework, or walking every day.

"These guidelines are an example of good government," says USDA Secretary Dan Glickman. "They will help consumers make informed food choices."

David B. Wasser of the Physicians Committee for Responsible Medicine, a group that advocates vegetarian diets, says that the guidelines "aren't everything that we hoped for" but notes that "for the first time, an agency which historically has been very biased toward the meat industry has acknowledged that vegetarian diets are healthful."

Although Michael F. Jacobson of the Center for Science in the Public Interest also appreciates that acknowledgment, he maintains that the guidelines "fail to recommend the best possible diet," which would be much lower in salt and fat. — *L. Seachrist*

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