

brain

BRIEFINGS

NOVEMBER 2007

WITH OBESITY NOW A MAJOR HEALTH EPIDEMIC, THE SEARCH TO UNDERSTAND THE BRAIN'S ROLE IN REGULATING APPETITE AND FOOD INTAKE HAS TAKEN ON A NEW URGENCY. RECENT YEARS HAVE SEEN AN EXPLOSION IN OUR KNOWLEDGE OF THE PATHWAYS THAT CONTROL OUR DESIRE TO EAT, WHICH, WHEN DISRUPTED, CAN CAUSE US TO PILE ON THE POUNDS. SCIENTISTS ARE BEGINNING TO TRANSLATE THIS KNOWLEDGE INTO PROMISING NEW TREATMENTS FOR OBESITY AND ITS RELATED DISEASES.

APPETITE AND FOOD INTAKE

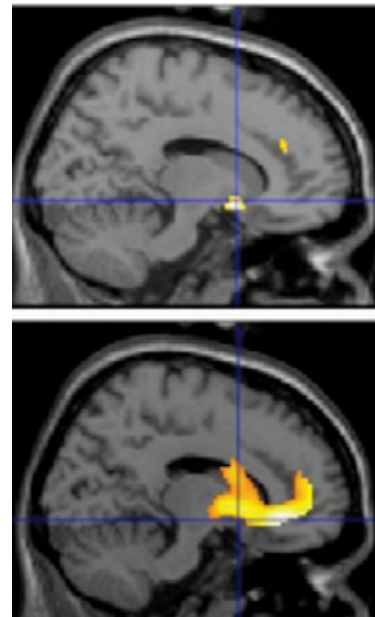
Anyone who spends any time people-watching—at a mall, at a sporting event, in the lobby of a movie theater—knows that we're in the midst of an obesity epidemic.

Two-thirds of Americans are now either overweight or obese. As our collective weight inches upward (and outward), so do our healthcare costs, for obesity raises the risk for many chronic and potentially life-threatening illnesses, including diabetes and heart disease. In the United States, we spend at least \$92.6 billion—or about 9 percent of total U.S. health expenditures—on obesity-related health problems.

Although a “cure” for obesity remains elusive, scientists are getting tantalizingly close. In recent years, they've unlocked many of the mysteries of the incredibly complex neurochemical feedback mechanisms that regulate our appetite and body weight. Such research is leading to:

- Greater knowledge of how and why people become obese.
- Insight into the effects that different diets have on weight regulation.
- A better understanding of the link between obesity and

▶ **THE HORMONE LEPTIN, WHICH IS PRODUCED IN THE BODY'S FAT CELLS, PLAYS A MAJOR ROLE IN APPETITE REGULATION, INCLUDING HELPING THE BRAIN DISCRIMINATE BETWEEN APPETIZING AND BLAND FOODS. THESE BRAIN SCANS ARE OF AN OBESE TEENAGER WHOSE FAT CELLS WERE UNABLE TO SECRETE LEPTIN. WHEN THE TEENAGER WAS GIVEN NORMAL LEVELS OF THE HORMONE, BRAIN IMAGING SHOWED GREATER ACTIVITY IN THE STRIATUM, AN AREA ASSOCIATED WITH REWARD, WHEN THE TEENAGER SAW APPETIZING FOODS (BELOW) THAN WHEN HE WAS LOOKING AT BLAND ONES (ABOVE). THE SAME PATTERN OF ACTIVITY FOR FOOD TYPES CAN BE SEEN IN PEOPLE WITHOUT A LEPTIN DEFICIENCY.**



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diabetes, heart disease, certain cancers, and other illnesses.

- Safer and more effective obesity treatments.

A major breakthrough in understanding the neuroscience of obesity came in 1994 with the discovery of the hormone leptin. Produced by the obese (ob) gene in the body's fat cells, leptin is largely responsible for the urge to eat. High levels of the hormone activate some of the brain's nerve cells, or neurons, in a way that suppresses appetite and creates a feeling of fullness. Low levels create a reverse message: hunger. Scientists now think that leptin may be even more critical than the hormone insulin in regulating the body's delicate balancing

act between calories in (eating) and calories out (exercise).

Exactly how leptin regulates appetite remains unknown, but new research has revealed that regions of the brain linked with pleasurable emotions and sensations—particularly the nucleus accumbens in the ventral striatum—jump into greater action at the sight of food when leptin levels are low. Yummier foods such as chocolate cake trigger greater activity than blander ones such as broccoli. Thus, leptin appears to control appetite in part by interacting with the reward areas in the brain that make eating enjoyable.

Scientists originally hoped that leptin could be used to treat obesity. But the story turned out to be much more complicated.

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Although morbidly obese people born without the ob gene do lose weight when given the hormone, such cases are very rare. Most obese people have the gene and produce plenty of the hormone—too much of it, in fact, causing them to become resistant to its effects. So they remain hungry, even after eating, say, a cheeseburger, double order of French fries, and a super-sized soft drink. Scientists are now attempting to identify the specific brain pathways and mechanisms associated with leptin resistance.

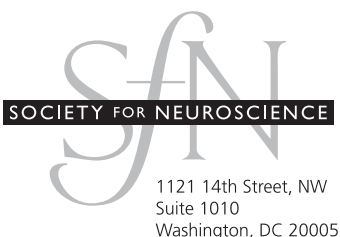
Another appetite-related hormone that has come under intense scrutiny is ghrelin, which is produced primarily in the stomach. Unlike leptin, ghrelin stimulates appetite—and quickly, on a meal-to-meal basis. Levels of the hormone rise rapidly in the bloodstream when the stomach is empty and

then race to tell the brain it's time to eat. As soon as the stomach becomes full and stretched, ghrelin levels fall. When people lose weight through dieting, their ghrelin levels become chronically high—which may explain why dieters struggle to keep weight off. Scientists are now looking to see if blocking ghrelin may help.

Yet another area of research involves the receptors, or “docking sites,” on neurons for the hormone melanocortin-4. When activated, these receptors help suppress appetite. When they become defective, however, they lead to morbid obesity. Recent research involving mice has revealed that activation of melanocortin-4 receptors in certain areas of the brain—the paraventricular hypothalamus and the amygdala—help reduce body fat by decreasing our desire to eat, while receptors

on neurons elsewhere in the brain help increase the amount of calories our bodies expend. This finding may lead to more targeted treatments for helping people control their weight.

Other research has uncovered differences in how the brains of men and women regulate appetite. Estrogen, for example, has been found to use the same pathways in the brain as leptin uses to suppress appetite—a possible reason why women tend to gain weight after menopause. Another study recently reported that the children of women who undergo gastric bypass surgery before becoming pregnant are only half as likely to become obese. This intriguing result suggests that both the genes and the environmental factors causing obesity can be overridden—further hope that the obesity epidemic may one day be brought under control.



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