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Obesity: It May Be How You're Wired

New studies by Howard Hughes Medical Institute researchers at The Rockefeller University show that the appetite-regulating hormone leptin causes rewiring of neurons in areas of the brain that regulate feeding behavior.

The discovery is another important clue about how leptin exerts its effects on the brain to cause decreased food intake and increased energy expenditure, said the researchers. The research also suggests that natural variability in the "wiring diagrams" of the neural feeding circuits of individuals may influence whether a person will be obese or lean.

The research team, which was led by Howard Hughes Medical Institute investigator [Jeffrey M. Friedman](#) at Rockefeller and Tamas L. Horvath at Yale University School of Medicine, published its findings in the April 2, 2004, issue of the journal *Science*.

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Friedman and his colleagues discovered leptin in 1994. They also showed that it is produced by fat tissue and secreted into the bloodstream, where it travels to the brain and other tissues, causing fat loss and decreased appetite. In the brain, leptin affects food intake by acting on distinct classes of neurons in the hypothalamus that express the leptin receptor.

Leptin decreases feeding and fat deposition by acting on two classes of neurons. Leptin suppresses the activity of neuropeptide Y (NPY) neurons and it enhances the activity of proopiomelanocortin (POMC) neurons. Conversely, the absence of leptin increases feeding and fat deposition by exciting NPY neurons and suppressing the activity of POMC neurons.

While the action of these two types of neurons had been inferred, said Friedman, there had been no direct studies exploring the specific mechanism by which leptin affected the neurons.

“There are a number of theoretical ways in which a molecule such as leptin might modulate the activity of neurons,” said Friedman. “And I’m sure it’s the case that leptin can act in many different ways. But what we have discovered is a particularly striking modality of action that wasn’t what we initially would have suspected was the likeliest.”

The major problem in studying in detail the action of leptin on NPY and POMC neurons was in distinguishing the two classes of neurons, said Friedman. “If you just look at a region of the brain, you can’t tell one neuron from the next,” he said. “And in this case, you had in one brain region neurons theorized to stimulate appetite right next to those believed to inhibit appetite.”

The solution, said Friedman, was to genetically engineer mice to have NPY and POMC neurons that each expressed a distinctive version of a green fluorescent protein. These fluorescent proteins literally lighted the way for the scientists to perform detailed studies of the action of leptin on the two neuronal types.

The researchers generated both normal mice and those deficient in leptin production—called *ob/ob* mice—containing the fluorescently labeled neurons. They then compared the neurons in the two strains of mice.

One of the co-lead authors in the *Science* paper—Aaron G. Roseberry in Friedman’s laboratory—compared the electrophysiological properties of the two types of neurons, in both normal and *ob/ob* mice. These studies revealed the relative activity of the two types of neurons in the two mouse strains.

Another co-lead author—Shirly Pinto in Friedman’s laboratory—worked with Horvath to perform comparative microscopy studies of the labeled neurons in the two strains of mice. These studies revealed the relative numbers of excitatory and inhibitory neuronal connections in the two types of mice.

Both sets of studies revealed that leptin acted directly to rewire the neuronal feeding circuitry itself in the brains of mice, specifically suppressing NPY neurons and exciting POMC neurons.

The researchers also found that administering leptin to the leptin-deficient *ob/ob* mice produced changes in neuronal connections—and their electrical activity—to mimic those of normal mice. The neuronal changes preceded the behavioral changes in the *ob/ob* mice. This is significant, according to Friedman, because it suggests a cause-and-effect relationship between the rewiring and feeding behavior.

Furthermore, when the researchers tested the effects of ghrelin, another appetite-stimulating peptide, on the two types of neurons in normal animals, they also observed a decrease in excitatory connections to POMC neurons. “Taken together, the findings with leptin and ghrelin suggests that the findings of this rewiring are general,” said Friedman.

“Overall, these findings begin to suggest that the wiring diagram of the feeding circuit is highly dynamic,” said Friedman. “And they lead us to at least ask to what extent is the wiring diagram of these neural circuits different in obese people relative to lean people.

“If we knew that the basic circuitry that controls feeding is wired differently in different people, it might change public perception of the causes of obesity,” said Friedman. “Some people might have a more potent drive to eat and to weigh more than do others. And it might mean that conscious factors can't fully explain how a person eats.”

Such findings might also contribute in time to a broader understanding of why administering leptin can reduce weight in some obese people and animals, but not in others. The variable response to leptin suggests that some individuals are obese because they are leptin resistant. Advances about how leptin works in the brain could contribute to a better understanding of leptin resistance and obesity, and may ultimately lead to new ways to combat obesity, said Friedman.