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Mutations in a Leptin Receptor Cause Obesity in Mice

The weight-reducing effects of leptin, a hormone that signals the size of the body's fat stores, result from interaction with a receptor in the brain's hypothalamus and other tissues, HHMI scientists at The Rockefeller University reported in the February 15 issue of *Nature*.

"When we found leptin in 1995, we suspected it acted in the hypothalamus, a region of the brain known to regulate food intake and body weight," said Jeffrey M. Friedman, a Hughes investigator at Rockefeller. "In our current work, we have determined that there are at least six different forms of the leptin receptor, known as Ob-R. One of these forms, Ob-Rb, is expressed at a high level in the hypothalamus and at lower levels in other tissues."

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Friedman and his colleagues have found Ob-Rb is mutant in spontaneously diabetic (*db*) mice, which are consequently massively obese and resist leptin treatment. While Ob-Rb appears to be critical for the weight-reducing effects of leptin, the functions of other forms of Ob-R are not known, Friedman said.

The scientists identified the Ob-R receptors by scanning for genes in the region of the *db* mutation on mouse chromosome 4. They found that one of the genes in this region was identical to the Ob-R gene. They observed, however, that the Ob-R gene can result in many different forms of the receptor.

"Leptin may modulate the activity of other peptides and neurotransmitters that are known to affect feeding behavior in the hypothalamus," Friedman explains. "Leptin also may affect other tissues that have Ob-Rb receptors, including fat."

Friedman's co-authors include Gwo-Hwa Lee, Ph.D., Ricardo Proenca, J. M. Montez, Kristine M. Carroll, Jerald G. Darvishzadeh, and Jung I. Lee.

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