

OCTOBER 01, 1995

Hormone Reduces Weight, Curbs Appetite and Accelerates Metabolism

In research that has captured the attention of the world and focused the media spotlight on the scientists involved, three independent laboratories have independently verified that a newfound hormone reduces body weight and speeds up metabolism.

The findings may have important implications for understanding the causes of obesity, but the authors note that new therapies for weight control will require many more years of studies and testing. "The current results suggest that the protein, leptin, is a novel hormone that regulates body weight by signaling the amount of fat stored," said senior author **Jeffrey M. Friedman** of HHMI at Rockefeller University. The name leptin is derived from the Greek root *leptós*, meaning "thin."

Friedman, with collaborator Stephen K. Burley, also of HHMI at Rockefeller University, and several coinvestigators found that leptin circulates in the blood of mice and humans. When administered to overweight mice during two weeks of treatment, recombinant leptin caused the mice to decrease food intake and increase energy expenditure. The mice lost about 30 percent of their body weight and almost all of their fat. Reports from two other research teams, one from the Amgen Corporation that has licensed the *ob* gene from Rockefeller University, and a second from Hoffmann-La Roche, corroborated the work of Friedman's group.

The three teams published their work simultaneously in the July 28 issue of *Science*. This latest research stems from the earlier cloning of the gene *ob*, which was reported by Friedman's group in the journal *Nature* last year. Data in the *Nature* article demonstrated that the instructions to make leptin are coded by a gene that is defective in the *obese (ob)* mouse. The *ob* mouse, long a staple of geneticists searching for molecular clues to obesity, was identified by scientists at the Jackson Laboratory in Bar Harbor, Me., in 1950.

Defects in the *ob* gene result in massive obesity in mice as part of a syndrome that resembles obesity in humans. "The new findings indicate that when *ob* is defective, leptin is not made and does not transmit its signal to tell the brain to stop eating," says lead author Jeffrey L. Halaas, a member of Friedman's team and a biomedical fellow at Rockefeller. Consequently, mice with a faulty *ob* gene are overweight and also have a form of diabetes.

In the *Science* paper, Friedman and colleagues measured the amounts of leptin in the blood of mice and found that those mice with a defective *ob* gene did not make the hormone. Another kind of overweight mouse that was also studied has a mutation in a gene called *diabetes (db)*. The *db*-defective mice had leptin levels 10 times higher than normal, bolstering the theory that these mice have an improperly functioning leptin receptor. The researchers also showed that leptin circulates in the blood of six lean humans who were studied.

In a four-week study, the scientists injected mouse leptin daily into sets of 10 *ob*, *db* and normal mice. The leptin was made in the laboratory by inserting the *ob* gene into bacteria. Each of the mice in the study received 5 milligrams of leptin per kilogram of body weight. For comparison, control mice received either injections of a salt solution or no treatment.

"The effect of laboratory derived leptin on food intake and body weight is dramatic," Burley said. After two weeks of treatment with leptin, the *ob* mice lost 30 percent of their body weight without any observable side effects. The reduced weight in these mice also came exclusively from fat loss. At the end of the study, treated *ob* mice had 9.1 grams of fat while untreated *ob* mice had 38.30 grams of fat. A normal, healthy adult mouse has between two and five grams of fat.

In contrast, leptin treatment had no effect on the *db* mice. "The failure of leptin to reduce body weight or food intake in *db* mice is consistent with earlier suggestions that these mutant mice are missing the leptin receptor and are thus resistant to the effects of the hormone," Friedman said.

Leptin treatment not only reduced food consumption in the *ob* mice, but also increased their energy expenditure. Four days after starting leptin treatment, the *ob* mice consumed about 60 percent less food than untreated *ob* mice. When untreated *ob* mice were placed on a low calorie diet in which they were fed only as much food as eaten by the treated *ob* mice, the food-restricted mice lost less weight — an 11 gram loss in dieting mice versus a 16 gram loss in mice receiving leptin. This result suggests that the protein also increases energy expenditure, Friedman said.

Both mouse and human leptin reduced body weight in the *ob* mice, raising questions of whether leptin might form the basis for a weight-reducing drug of the future. Friedman answers cautiously: "The fact that human leptin reduces weight in the mice raises the possibility that giving leptin to people might have similar effects. However, we must proceed cautiously to prove that the protein treatment is safe in animals. Studies in humans cannot begin until the protein has been confirmed to be without side effects."

Friedman, Halaas and Burley's coauthors include: Ketan S. Gajiwala; Margherita Maffei; Steven L. Cohen, a graduate fellow; and Brian D. Chait, all of Rockefeller; Daniel Rabinowitz, of Columbia University; and Roger Lallone of Brookwood Biomedical in Birmingham, Ala. Gajiwala also has an appointment with HHMI.