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HEALTH JOURNAL

By MELINDA BECK



Can't Keep the Weight Off? Maybe Leptin Is the Culprit

July 8, 2008; Page D1

So, you ate less and exercised more and lost weight. But now the pounds are piling back on. You're hungrier than ever, and you can't seem to resist food. Once again, it's all your fault, right?

Wrong. Blame evolution, and the fact that for the vast majority of human history, famine was a bigger threat than flab. Even your seeming lack of will power is part of a complex biological system that drives humans who have lost weight to regain it, according to new brain-scan research by scientists at Columbia University Medical Center.

YOUR QUESTIONS ANSWERED



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"Loosely put, after you've lost weight, you have more of an emotional response to food and less ability to control that response," says Michael Rosenbaum, lead author of the study in this month's Journal of Clinical Investigation.

Clinical Investigation.

The key driver of this system is leptin, a hormone secreted by fat cells. When humans (and rodents) lose 10% or more of their body weight, leptin falls rapidly and sets off a cascade of physiological changes that act to put weight back on. Skeletal muscles work more efficiently, thyroid and other hormones are reduced -- all so the body burns 15% to 20% fewer calories, enough to put back 25 pounds or more a year.

This mechanism kicks in whether people are obese or relatively lean before losing weight -- and researchers believe the effect can last for years. In previous studies, giving subjects replacement leptin reversed the metabolic changes, in effect tricking the body into ignoring the weight loss.

The latest study shows that these metabolic changes are mirrored in altered brain activity when people lose weight. The Columbia researchers put six obese subjects on liquid diets and reduced their weight by 10%, then gave them replacement leptin or a placebo. At each stage, researchers observed their brain activity using functional MRIs when they were shown food and non-food items.

DISCUSS



Have you found it harder to keep weight off than to lose it? Have you found ways to overcome this biological drive to regain? [Share your experiences.](#)

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[Read an article](#) from The Journal of Clinical Investigation on how leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. [See specific scans](#) that show changes in the brain.

The scans showed that in the weight-reduced state, the subjects had more blood flow in areas of the brain that govern emotional and sensory responses to food and less in areas

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- Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli; J. Clin. Invest. Michael Rosenbaum, et al. 118:2583 doi:10.1172/JCI35055
- Revisiting leptin's role in obesity and weight loss; J. Clin. Invest. Rexford S. Ahima, et al. doi:10.1172/JCI36284

involving control of food intake. When the subjects were given replacement leptin, brain activity returned to what it had been before they lost weight.

There are still many unknowns about how blood flow in the

brain corresponds to behavior. "I can't look at these scans and say, in 30 seconds, you're going to eat a banana," says Rudolph Leibel, a co-author of the Columbia study who helped discover leptin in the 1990s at Rockefeller University. Still, he says, the brain images provide further evidence of the powerful biological forces that send humans into survival mode, mentally and physically, when food is scarce and fat stores decline. "These people act as if they are hungrier, and combined with reduced energy expenditure, that's the 'perfect storm' for gaining weight."

Dr. Leibel also says that people should understand that regaining lost weight "is not free will. It's biologically determined and the species that didn't have this are the ones you see in the Museum of Natural History." It's only been in recent decades that this mechanism is contributing more to obesity than survival. "Now, anyone can summon an unlimited amount of food just with a cellphone," he says.

Scientists originally thought leptin might be harnessed as a weight-loss drug. Amylin Pharmaceuticals Inc. continues to research that possibility and is in Phase 2 trials of a combination of leptin and pramlintide, a diabetes drug. But leptin may hold more promise in helping to keep weight off, an area that the Columbia researchers say deserves more attention.

How do some people manage to overcome the leptin effect and keep weight off? Generally by watching their food intake very carefully and continuing to increase their physical activity. "Anybody who has lost weight and kept it off will tell you that they have to keep battling," says Dr. Rosenbaum. "They have essentially reinvented themselves, and they are worthy of the utmost admiration and respect."

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