UT SOUTHWESTERN MEDICAL CENTER NEWS

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EMBARGOED UNTIL 4 P.M. CDT THURSDAY, AUG. 23, 2007

Despite overeating, morbidly obese mice gain protection against diabetes

DALLAS – Aug. 23, 2007 – The "world's fattest mice" can overeat without developing insulin resistance or diabetes thanks to a glut of a key hormone, a dichotomy that helps explain why not all obese people are diabetic, a UT Southwestern Medical Center researcher has found.

Consuming excess calories usually spurs insulin resistance and diabetes. But in a multicenter study appearing online today in the *Journal of Clinical Investigation*, scientists show how an abundance of adiponectin, a hormone that controls sensitivity to insulin, and a lack of leptin, a hormone that curbs appetite, enables mice to store excess calories in fat tissue instead of in liver, heart or muscle tissue – places where excess fat can lead to inflammation, diabetes and heart disease.

The mice get morbidly obese, but are insulin-sensitive with normal blood-glucose levels.

"The message isn't that it's good to be obese, but that expanded fat mass, when stored in the right places, can help prevent diabetes and reduce the risk of heart disease," said Dr. Philipp Scherer, professor of internal medicine and the study's senior author. "In fact, these are the first mice to directly show that fat-mass expansion has antidiabetic effects." Dr. Scherer directs the Touchstone Center for Diabetes Research at UT Southwestern.

Fat tissue, which was largely perceived as a useless storage bin until the early 1990s, has been found to release hormones, including adiponectin, that play integral roles in metabolism and obesity. Adiponectin levels decline as a person accumulates more fat, making the levels a good predictor of future risk of developing diabetes, heart disease and cancer, said Dr. Scherer, who discovered the hormone in 1994.

But what would happen if, despite overeating, adiponectin levels increased?

To find out, Dr. Scherer and other researchers in this study genetically engineered mice to produce an overabundance of adiponectin while lacking leptin. Without leptin's signals to stop eating or burn energy, the mice continually consumed food and their weight ballooned.

The high levels of adiponectin, however, made the mice physiologically skinny, Dr. Scherer said.

"The continual firing of adiponectin generated a 'starvation signal' from fat that says it is ready to store more energy," he said. "The mice became what may be the world's fattest mice, but they have

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normal fasting glucose levels and glucose tolerance.

"This indicates that the inability to appropriately expand fat mass in times of overeating may be an underlying cause of insulin resistance, diabetes and cardiovascular disease."

This discovery also suggests that in people who have low adiponectin levels fat cells don't send the signal that they're ready to accept fat, Dr. Scherer said. Instead, the fat is stored in dangerous places – liver, heart and muscle tissues – where it can cause inflammation and pave the way for disease.

"More than 66 percent of American adults are overweight or obese, so most people have excess caloric intake. We need to find ways to deposit these calories in the least harmful places, because the fat has to go somewhere," he said. "For instance, people with excess weight around their abdomen run a higher risk of heart disease and diabetes than those who have excess weight in the thighs."

Dr. Scherer's next goal is to investigate how to manipulate individual areas of fat to find ways to maximize the "good" fat areas and shrink the "bad" areas. Researchers also could try to develop new disease treatments that don't require shedding fat.

"Until then, exercise and reduction of food intake are the best ways to stay healthy," Dr. Scherer said.

Researchers with the Albert Einstein College of Medicine, Laval University in Canada, the University of Cincinnati and Yale University School of Medicine also contributed to the study.

The National Institutes of Health, the New York Obesity Research Center and the Skirball Institute of Biomolecular Medicine supported the study.

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