SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS FIND LEPTIN TURNS FAT-STORING CELLS INTO FAT-BURNING CELLS

DALLAS – Feb. 9, 2004 – Increasing leptin, a protein involved in regulating body weight, in laboratory animals transforms fat-storing cells into unique fat-burning cells, researchers at UT Southwestern Medical Center at Dallas report. They speculate that these findings could provide "a quick and safe solution" to the obesity problem in humans.

Researchers attribute the change in the cell's structure and function in rats – from fat storing to fat-burning – to a massive increase in the action of mitochondria, the principal energy source of the cell. The increase in mitochondria, which also led to substantial weight loss in the rats, was found two weeks after researchers injected the *leptin* gene.

Findings from the study will appear in an upcoming issue of the *Proceedings of the National Academy of Sciences* and are currently available online.

"This is the first careful examination of the fat cells after leptin therapy," said Dr. Roger Unger, director of the Touchstone Center for Diabetes Research at UT Southwestern, a physician at the Dallas Veterans Affairs Medical Center and the study's senior author. "The structure of the cells changed from the normal appearance of a fat cell to a very novel cell that's really never been seen before. There's no precedent for a cell that appears like this.

"The ability to convert fat cells into fat-burning cells may suggest novel therapeutic strategies for obesity."

Dr. Unger and his collaborators began working on this research in 1996. During the initial phase of the study, Dr. Unger observed that the fat had disappeared in the fat cells, but at that time the researchers could only guess why.

"We predicted this in 1996, but until we showed the increase in mitochondria there was not any proof of what was happening, but there were many clues that the fat was being burned inside the cell," Dr. Unger said.

Collaborating with researchers at the University of Geneva Medical School, who conducted morphological tests to analyze the form and structure of the cells, the scientists found

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in the current study that instead of containing fat, the cells were crowded with mitochondria.

Researchers examined laboratory animals weighing between 280 grams (a little more than half a pound) and 300 grams. Some of the study subjects received an intravenous injection of the *leptin* gene, which was expressed in and produced by the liver; leptin level rose 50 times greater than normal in rats after two to four days before tapering off. The remaining laboratory animals followed a restricted diet.

Animals receiving the injection experienced a rapid and profound loss of fat compared to the animals that followed a restricted diet.

"After 14 days, rats receiving leptin injections plummeted on average from 280 to 207 grams," Dr. Unger said, or about 26 percent of total body weight.

While the rats receiving the leptin injections were healthy, active and had a decreased appetite, the animals that followed a restricted diet were constantly searching for food and experienced reduced physical activity.

The animals fed a restricted diet also gained back their weight faster than animals receiving the leptin injections.

Under normal circumstances leptin produced by fat cells does not interfere with the accumulation of surplus fat, but leptin secreted by the liver does interfere with the fat and actually causes the surplus to burn up, Dr. Unger said.

"We would like to break down the normal defense system against leptin produced in the fat cell. If we could disable or bypass this system and transform fat (storing) cells into fat-burning cells, then we may be a step closer to solving the obesity epidemic."

Other UT Southwestern researchers who contributed to the study were Dr. William Cook, a postdoctoral researcher in surgery; Dr. Byung-Hyun Park, a postdoctoral researcher in internal medicine; and Dr. May-Yun Wang, an instructor of internal medicine.

The study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases and the Swiss National Science Foundation.

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