SOUTHWESTERN NEWS

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GENE THERAPY USED TO CREATE RATS WITH NO FAT

DALLAS – Dec. 10, 1996 – Healthy rats with no visible body fat have been created by UT Southwestern Medical Center at Dallas scientists. Using gene therapy, they made the animals overproduce the controversial hormone leptin.

The researchers made the animals' bodies manufacture 20 times the normal amount of the fat-controlling hormone by using a virus to insert the leptin gene. They discovered that the rodent's insulin levels dropped by more than half, yet they did not develop diabetes. This finding is in contrast to another recently published study that suggested high leptin levels might cause diabetes.

"This is the first time that animals have been produced which are free of body fat yet remain in perfect health," said Dr. Kazunori Koyama, a UT Southwestern research fellow in internal medicine and one of the authors of the study published in today's *Proceedings of the National Academy of Sciences*.

"In other conditions of extreme thinness and fat loss -- like starvation, severe diabetes or severe hyperthyroidism -- the animals also lose lean body mass. But not in these; they selectively lose fat," Koyama said.

Researchers hope these findings will help them determine what role fat plays in various bodily functions and diseases, including type II diabetes (non-insulin dependent diabetes mellitus). Obese adults often contract the disease.

Dr. Robert O'Doherty, another of the study's authors and a UT Southwestern fellow in biochemistry, cautioned, "This is not a treatment for human obesity. We don't yet know the long-term effects of leptin. Also, obese people already have high leptin levels. The reason they are not losing weight may be that they are resistant to leptin."

Koyama said previous studies have shown that daily injections of leptin have caused weight loss in obese animals, but the rodents became unhealthy because both fat

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and muscle were depleted.

Hyperleptinemic rats are easily distinguishable from normal rats with normal food intake and from healthy, unaltered rats on the same diet as the nonfat rats, Koyama said. The genetically engineered rodents are very thin but not emaciated, and they are very active, almost as if they have hyperthyroidism. The hyperleptinemic rodents are uninterested in food; they eat about 30 percent less food than a comparable animal.

Rats given the same type and amount of food as the hyperleptinemic rodents appear fatter, are less active and constantly search for food.

"These animals are the antithesis of obesity," O'Doherty said. "They can be compared most closely to human gymnasts who have almost no body fat but are in prime physical condition."

The researchers, working in the Gifford Laboratories for Diabetes Research at UT Southwestern and at the Dallas Veterans Affairs Medical Center, infused a recombinant adenovirus with the leptin gene into healthy 9-week-old rats with normal body fat. The animals overproduced leptin, which caused them to lose all body fat around their organs and under their skin.

The rodents were studied for 28 days, after which the average weight of the rats that received the leptin gene was about 100 grams less than the comparable control animals. Although leptin is usually produced only in fat cells, the scientists found that the nonfat animals were producing the hormone in their livers because the virus settled there. The effect of the leptin lasted only about four weeks.

An interesting result of the research was that the hyperleptinemic rats had insulin levels 60 percent lower than did the animals with normal levels of the fat-controlling hormone, yet their blood-glucose levels remained normal. Researchers suspect that an animal's sensitivity to insulin may be linked to its amount of body fat.

Other researchers involved in the study were Dr. Roger Unger, director of the Gifford Laboratories and holder of the Touchstone/West Distinguished Chair in Diabetes Research; Dr. Christopher Newgard, professor of biochemistry and internal

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medicine and holder of the Gifford O. Touchstone Jr. and Randolph G. Touchstone Distinguished Chair in Diabetes Research; Dr. Young Lee, assistant instructor of internal medicine; Guoxun Chen, a research fellow in internal medicine; and Xue Yuan, a technician.

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