Studies on a Mouse Hormone Bear on Fatness in Humans

By GINA KOLATA Published: April 2, 2004

New studies in mice suggest that the hormone leptin can fundamentally change the brain's circuitry in areas that control appetite. Leptin acts during a critical period early in life, possibly influencing how much animals eat as adults. And later in life, responding to how much fat is on an animal's body, it can again alter brain circuitry that controls how much is eaten. Researchers say the findings, published today in the journal Science, are a surprise and add new clues to why weight control is so difficult in some humans

Scientists knew that leptin is released by fat cells and tells the brain how much fat is on the body. They knew that animals lacking leptin become incredibly obese, as do a few humans who because of genetic mutations did not make the hormone. Leptin injections immediately made animals, and the patients with leptin deficiencies, lose their appetites. Their weight returned to normal. But it was thought that leptin acted like most other hormones, attaching itself to brain cells and directly altering their activities.

Investigators did not anticipate that leptin could actually change connections in the brain, strengthening circuits that inhibit eating and weakening ones that spur appetite. And few considered the possibility that there might be a critical period early in life when the hormone shaped the brain's circuitry, possibly affecting appetite and obesity in adulthood.

"It's fascinating," said Dr. Rudolph Leibel of Columbia University. "Obviously, we don't know what this looks like in humans, but it is possible that some of the differences in regulation of body weight that have been attributed to psychological processes or fat cell effects may be reflecting these central nervous system processes."

Dr. Jeffrey Flier of Beth Israel-Deaconess Hospital in Boston said the effects of leptin reminded him of brain changes when memories are stored. It is almost as if the brain is developing a memory for the weight it wants the animals to be, Dr. Flier said, raising intriguing possibilities about weight regulation in people.

"It all comes back to the same issues — the whole issue of appetite and weight regulation in humans," Dr. Flier said. "It is at the interface of free will and determinism. There is certainly a strong biological underpinning to our drive to eat and maintain certain weights. We knew that before and we still know it.

"But now there is another layer of mechanisms by which things like hormones not only can affect the neurochemistry that affects how hungry you are but also can affect the wiring of your brain."

In the first of two papers in Science, Dr. Richard B. Simerly and Dr. Sebastian G. Bouret at the Oregon Primate Research Center in Beaverton examined leptin's effects on the brain early in life. Until now, they had studied how sex hormones, like estrogen and testosterone, affected brain development.

But they noticed an earlier paper by Dr. Flier showing that there is a surge of leptin in the brains of newborn mice, looking a lot like the surges of sex hormones that reshape the brain during critical periods early in development. Could leptin, they asked, be doing something similar?

"Bingo," Dr. Simerly said. "The lights went on."

As adults, mice with a genetic mutation preventing them from making leptin had weaker nerve connections in the arcuate nucleus of the hypothalamus, which controls eating behavior and develops soon after birth. Perhaps, Dr. Simerly said, if he gave the leptin-deficient mice a surge of leptin early in life, mimicking what normal mice experience, he could reshape their brains, making them look like those of mice without the genetic defect.

It worked, Dr. Simerly and Dr. Bouret reported, raising questions about what happens normally during development in mice, and people, that might determine whether they were destined to be fat or thin.

"Leptin acts on the brain to regulate food intake," Dr. Simerly said. "If the brain pathway isn't there or is greatly reduced, you would expect that process to be deficient. Your brain is perhaps not sensing how fat you are."

In the second paper, by Dr. Jeffrey M. Friedman, a Howard Hughes medical investigator at Rockefeller University, he and his colleagues examined two brain pathways in adult mice — one that increases appetite and another that decreases it. By examining the actual nerves in slices of brain, they said, they saw that mice that make no leptin have strong brain circuits that signal them to eat. They have correspondingly weak circuits that signal them to stop eating.

Then they gave the animals leptin. Within six hours, their brain circuits were like those in normal animals, the researchers said. Two days after being treated with leptin, the mice lost their huge appetites.

The researchers also tested another hormone, ghrelin, whose effects are the opposite of leptin's, giving it to normal mice. Four days later, the animals were eating more and their brains were rewired in the opposite direction, the researchers said. Dr. Friedman said he was taken aback.

"I'd always imagined this system had a fixed architecture, like a plumbing system," he said. "A certain number of pipes were laid out or fixed." He said he had thought the flow of signals in the hypothalamus was regulated by the equivalent of opening or closing valves. But that was not what happened.

"In this case, the brain is adding and subtracting pieces of pipe," Dr. Friedman said. "Nerves are not appearing or disappearing, but the way they are connected to each other is.

"Right now there is an assumption on the part of the public that differences in weight are accounted for by discipline."

It is thought, he said, that with will power, anyone can lose weight and keep it off.

"That assumes that the drive to eat is the same in all people," Dr. Friedman said, "but this says there is not only a dynamic system that controls weight but that the wiring diagram is different in the obese. It at least raises the question, To what extent is the wiring diagram different in obese humans?"