In obesity, brain becomes 'unaware' of fat

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Critical portions of the brain in those who are obese don't really know they are overweight, researchers have reported in the March issue of the journal *Cell Metabolism*, published by Cell Press. These findings in obese mice show that a sensor in the brain that normally detects a critical fat hormone—causing a cascade of events that keeps energy balance in check—fails to engage. Meanwhile, the rest of the metabolic pathway remains ready to respond.

"Obesity is not a failure of will power, it is a biological failure," said Michael Cowley of Oregon Health & Science University of his group's findings in the mice. "The brain is not aware that the body is obese."

If the same is true in humans, he added, people may be consciously aware that they are overweight, but "that's different from the homeostatic circuitry being aware."

The new results also bolster evidence that a suppressor called SOCS-3 may be responsible for the loss of sensitivity to the fat hormone known as leptin. Therapeutic strategies designed to inhibit SOCS-3 may therefore bypass leptin resistance in obese animals to restore energy balance, according to the researchers.

In most adults, body weight is relatively constant despite large variations in daily food intake and energy expenditure, Cowley explained. Energy balance is regulated by neural and hormonal signals that are integrated in the brain.

Leptin sends signals to the brain about the body's fat reserves, modifying appetite and energy expenditure accordingly. The arcuate nucleus in the brain's hypothalamus, known as the ARH, is a major site of leptin sensing, harboring neurons that control appetite.

More than 60 percent of American adults are now overweight or obese, and obesity prevalence in both adults and children is growing dramatically. When scientists first discovered leptin, it was heralded as a potential obesity cure, Cowley said. If obese individuals lacked normal leptin levels, simply restoring the hormone might have been a means for weight loss.

It soon became clear that there was a problem: obesity isn't the result of a lack of leptin, but rather a lack of leptin response. In fact, obese individuals tend to have high levels of circulating leptin.

"They have enough, but it's not doing its job," Cowley said. "It's an example of classic hormone resistance."

Cowley's group set out to show exactly where that breakdown occurs. The researchers fed mice a high-fat diet for 20 weeks, a long time for the mice, which live only for a couple of years. For reasons that remain unclear, some of the genetically identical mice became obese when fed such a diet, while others did not.

"On a high-fat diet, not all of the animals become fat," Cowley said. "About 60 percent become fat, while others on the same diet, same calories, don't gain weight, and leptin levels remain normal. Something else must protect them."

The animals that did become obese maintained normal levels of the ARH brain receptors that respond to leptin, the researchers showed, while the level of SOCS-3 rose. Leptin hormone in those heavy animals

failed to elicit “any element of the leptin signaling cascade.” The researchers demonstrated that those later players in the leptin pathway remained ready for action. Indeed, the downstream factors were actually found to be hypersensitive to stimulation.

“Previous studies have suggested that SOCS-3 is a negative regulator of leptin,” Cowley said. “As animals become bigger and fatter and leptin increases, SOCS-3 may rise to decrease the signal. It seems that in obesity, SOCS-3 might end up overriding the [leptin] signal completely.”

When the amount of fat in the animals’ diets was reduced—even without any reduction in calories—the mice continuously lost weight until they reached a size comparable to control animals. Their brains’ appetite control centers also regained sensitivity to leptin.

“That was a surprise, a nice surprise,” Cowley said. “We had thought it might be more irreversible than that.”

However, Cowley cautioned, previous studies in humans haven’t always supported the idea that reducing fat intake alone has a major effect on obesity, noting that the digestive systems of mice and humans differ substantially. His team has plans to examine these effects in overweight primates, whose digestive systems have much more in common with people.

The findings do “strongly support the case” that leptin resistance in critical brain regions is a cause of obesity induced by diet, the researchers concluded. The results also “strongly validate” SOCS-3 as a target for antiobesity drug development.

Source: Cell Press