MedicalXpress

Study pinpoints how genetic glitch could keep some people from feeling full

July 31 2006

Nearly 6 percent of morbidly obese children and adults have a genetic defect that keeps them feeling like their stomach is running on empty, no matter how much they have eaten.

Mutations of the melanocortin-4 receptor, a gene found in brain cells that play a role in regulating hunger, are the most common cause of genetic obesity. Now University of Florida researchers have determined how some of these mutations cause the receptor to miss signals from molecules that tell the body when to eat and when to put down the fork, placing scientists one step closer to finding a way to correct these defects.

In a side-by-side comparison of 40 genetic mutations, UF medicinal chemists found that 11 caused the receptor to behave abnormally, according to findings recently published in the online edition of the journal Biochemistry.

The goal is to discover the molecular glitch that causes the receptor to malfunction so chemists can make drugs to treat it, said Carrie Haskell-Luevano, Ph.D., a UF associate professor of medicinal chemistry and the study's lead author. UF researchers have already found a molecule that seems to correct one of the mutations, keeping the hunger-signaling pathway running smoothly, Haskell-Luevano said.

"If you administer these compounds, it's a potential anti-obesity agent because you feel full," Haskell-Luevano said. "On the other hand, if you

have cancer or wasting disease, if you administer an antagonist that blocks or turns off the system, then you want to eat or you feel hungry.

"It directly controls the desire to eat."

About 30 percent of adults and 16 percent of children in the United States are overweight, according to the Centers for Disease Control and Prevention. Only a fraction of these people have genetic conditions or mutations that are linked to obesity, but researchers say studying genetic obesity can also help uncover clues to treating the nation's growing weight problem.

"There are so many factors that come into play," Haskell-Luevano said. "It's a very simplistic approach to say what we study in a dish (completely explains) why a person is obese. At the same time, taking it down to the simplest level is how you identify specific problems."

The melanocortin-4 receptor's link to obesity was first reported in 1997 when scientists discovered that a mouse missing the protein that turns on the receptor was obese, ate more than other mice and had developed type 2 diabetes.

Scientists then made a connection in humans, discovering that some morbidly obese children and adults had mutations in the receptor at the DNA level. Since then, about 60 separate mutations have been found, Haskell-Luevano said.

"Understanding this pathway is really important to understanding obesity," said Sadaf Farooqi, M.D., a Wellcome Trust clinician scientist fellow at Cambridge University who was part of a team of British scientists who made the connection between the melanocortin malfunction and obesity in humans. "(This study) provides more detail and it starts to put some of the pieces of the puzzle together. It's an

important part of getting to the next step."

UF researchers spent three years collecting data from cells, studying how mutated receptor cells reacted to the molecules that normally stimulate the body to eat or stop eating, said Zhimin Xiang, M.D., a UF biological scientist who led the experiment. Now, researchers are preparing to study mice that have been injected with the same genetic mutations they have been observing in a dish, to see if these defects cause the animals to become obese, Xiang said.

UF scientists are also trying to understand why exercise keeps the hunger-signaling system working. Emerging evidence shows that running on a wheel seems to keep melanocortin-4 receptor deficient mice from becoming obese and diabetic, Haskell-Luevano said.

But until scientists can find a way to treat the problem, Haskell-Luevano encourages people to be a little less judgmental of obese children and adults, who may be struggling with a problem they cannot control.

"Genetics is a very strong component of obesity," she said. "As a scientist and a researcher, what I like to focus on is seeing if we can design some molecule or drug that can fix this."

Source: University of Florida