# Rare syndrome provides clues on obesity, blood pressure

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University of Iowa researchers have found a clue about how resistance to the hormone leptin might disrupt the brain signals that tell the body when to stop eating. The research, which focused on the rare genetic disorder Bardet-Biedl syndrome (BBS), also found an association between leptin resistance and high blood pressure.

The findings, which were based on mouse models developed at the UI, have implications for treating BBS as well as obesity and high blood pressure in people without BBS. The study appeared online March 3 in the *Journal of Clinical Investigation*.

"Bardet-Biedl syndrome is rare but its symptoms, including obesity and increased risk of heart disease, are similar to problems faced by many people without the syndrome," said Kamal Rahmouni, Ph.D., the study's principal investigator and assistant professor of internal medicine at the UI Roy J. and Lucille A. Carver College of Medicine. "Leptin normally suppresses appetite and increases caloric use. The more we know about how leptin and gene defects affect people with BBS, the more likely it is that we can improve treatment for them and people with similar symptoms."

The research builds on previous BBS findings, including research led by current study team member Val Sheffield, M.D., Ph.D., the Martin and Ruth Carver Chair in Genetics and professor of pediatrics at the UI and a Howard Hughes Medical Institute investigator.

Fewer than one in 10,000 people have BBS. Sheffield, who has discovered or co-discovered the majority of the 12 known BBS genes, developed BBS mice that have the same features as the human condition. The study used a mouse model without BBS and three mouse models that each lacks a protein (Bbs2, Bbs4 or Bbs6) due to a BBS gene deletion.

The team measured daily food intake and body weight of each mouse. Some mice also received daily leptin injections. Mice without BBS lost weight when injected with leptin. However, the mice with any of the three types of BBS gene defects did not respond to leptin and gained weight.

Rahmouni, who has expertise in metabolism and obesity, said the hormone leptin is an obvious candidate when looking at causes of weight gain.

"Leptin is made in adipose (fat) tissue and is supposed to decrease fat stores. However, if we find high levels of it in the plasma, and people still are obese, we know it's not acting correctly and that there is leptin resistance," he said.

The team also found that even very young mice with BBS, whose body weights were the same as the non-BBS mice, had high levels of leptin in the plasma, indicating leptin resistance. The team then looked at a specific brain region of mice with BBS to understand why this occurred.

"We know that leptin regulates body weight and food intake through the hypothalamus in the brain. In the mice with BBS, we saw that Pomc, one of the three main genes normally regulated by leptin, was not properly regulated," Rahmouni said.

"This finding allowed us to pinpoint a very specific defect that explains

why these mice are obese. The brain normally uses the Pomc gene to tell the body to stop eating, but in the animals with BBS, it doesn't work and so the mice won't feel full. We know that people without this gene have the same symptoms as the mice in our study, so the finding is meaningful," he added.

Rahmouni and colleagues will next examine the specific deficit in the neurons in the brain that might cause the problem with the Pomc (pronounced "pom-c") gene.

In another aspect of the study, the team saw that two of the three mouse models with BBS protein problems (Bbs4 and Bbs6) had high blood pressure. Recent research published by another institution has pointed to the same problem in humans with the same gene defects.

The UI team found that using a chemical to block neurotransmission in mice with the Bbs4 and Bbs6 gene defects lowered blood pressure.

"Because there are so few people with BBS, mouse models are very helpful in trying to understand the blood pressure problem," Rahmouni said. "Currently, there is no specific recommendation on what drug or level of drug to use to treat hypertension in BBS patients. In addition, this work may lead to improved treatment of hypertensive patients without BBS. We hope to learn more about the mechanism in order to improve and even customize treatment."

Source: University of Iowa