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Major link in brain-obesity puzzle found

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A single protein in brain cells may act as a linchpin in the body's weight-regulating system, playing a key role in the flurry of signals that govern fat storage, sugar use, energy balance and weight, University of Michigan Medical School researchers report.

And although it's far too early to say how this protein could be useful in new strategies to fight the world's epidemic of obesity, the finding gives scientists an important system to target in future research and the development of anti-obesity medications.

In the February issue of the *Journal of Clinical Investigation*, U-M researcher Liangyou Rui, Ph.D. and his team report their findings on a protein called SH2B1, and specifically on its activity in brain cells.

Using a variety of genetic, diet and hormone techniques, they were able to show that the action of SH2B1 regulates body weight, the action of the metabolic signaling molecules leptin and insulin, and the use of energy from food. It even moderated the impact of a high-fat diet on body weight.

The experiments were performed in mice, including two types of mice that the team altered genetically so that they only expressed a unique form of the SH2B1 protein in their brain cells. The protein occurs elsewhere in the body, but the researchers were able to zero in on its activity in the hypothalamus: the area of the brain that coordinates signals from the brain and body relating to food, hunger, and the balance of energy and nutrients in the body.

Previously, Rui and his team have shown that mice that lack the gene for SH2B1 -- called knockout mice -- become obese, diabetic, and unable to stop eating. Their bodies lose the ability to sense the signals sent by leptin and insulin that tell the brain to slow down food intake and fat storage.

For the new paper, they looked at not only normal mice and mice that didn't have the SH2B1 gene, but also at mice that made SH2B1 only in brain cells, either in normal or larger-than-normal amounts. They found that restoring SH2B1 just in the brain completely corrected the metabolic disorders that the knockout mice had developed, but also improved the brain cells' ability to respond to leptin signals and produce further signals that regulate eating.

What's more, the mice that were treated to make extra SH2B1 didn't become obese or lose their ability to respond to leptin signals even after being fed a high-fat diet that caused those effects in other mice.

"Obesity, whether in mice or humans, is the product of an altered balance between energy intake and energy use. The imbalance is linked to alterations in leptin and insulin signaling that lead to excess weight gain and Type 2 diabetes, respectively," says Rui, an assistant professor of molecular and integrative physiology at U-M. "SH2B1 appears to play a key regulatory role in this system, through its direct influence on the processing of leptin and insulin signals in cells of the brain's hypothalamus."

Rui, who first discovered SH2B1's metabolic importance as a graduate student at U-M in the 1990s, worked on the new paper with postdoctoral fellow Decheng Ren, Ph.D., who also collaborated on a paper in the journal Cell Metabolism in 2005 that first indicated SH2B1's key role in obesity.

The team and other researchers have found that SH2B1, which was previously called SH2-B, is a kind of jack-of-all-trades in the world of cell signaling. Able to shuttle between the area just beneath the cell membrane and the nucleus, it can bind to many different molecules and facilitate signaling.

Specifically, it can bind to a variety of molecules called tyrosine kinases, including ones that serve as receptors for insulin and growth factors that circulate in the brain and body. One of its most important binding partners is JAK2, which is activated every time a leptin molecule binds to a cell.

Since leptin is the body's messenger boy to the brain for "stop eating, we're full" messages, and JAK2 helps receive those messages as they arrive, SH2B1's partnership with JAK2 is an important one. In a previous paper, Rui and his former mentor and current colleague Christin Carter-Su, Ph.D., showed that SH2B1 encourages the action and production of JAK2, unlike two other proteins that have been shown by other teams to reduce its activity. Carter-Su is a professor of molecular and integrative physiology and heads the biomedical research division of the Michigan Diabetes Research and Training Center.

In addition to revealing the importance of SH2B1 activity in the brain, the new paper shows that SH2B1 is expressed in four different forms in many tissues of the body, including fat cells known as adipose tissue, as well as the liver, heart, pancreas and muscle.

Rui and his team also explored the role of SH2B1 in fat cells, finding that the knockout mice that lacked the SH2B1 gene stored away much more fat than normal mice, and had much larger fat cells – giving them two-and-a-half times more body fat content than normal mice. The mice that had some of their SH2B1 restored in just their brains by genetic alteration did not experience this – and in fact had less fat than normal

mice.

Since these mice lacked the ability to make SH2B1 in their fat cells, the authors suspect that fat-cell SH2B1 encourages the storing of fat. When they tested this theory, they found that SH2B1 appeared to help mouse embryonic cells turn into fat cells, a process called adipogenesis. But, they suspect, the action of SH2B1 in the brain trumps its action in fat tissue, leading to the development of obesity in mice that lack SH2B1 in both locations.

Rui and his team now hope to explore SH2B1's role in the brain and body even further, and hope to translate their findings into clinical research involving humans. They hope that their findings will help lead to better tactics for understanding the causes of obesity and its consequences, including Type 2 diabetes, and perhaps better methods for preventing and reversing them.

Source: University of Michigan Health System