

Research team discovers brain pathway responsible for obesity

October 2 2008

University of Wisconsin-Madison researchers, for the first time, have found a messaging system in the brain that directly affects food intake and body weight.

Reported in the Oct. 3, 2008 issue of *Cell*, the findings--from a study in mice--point to a completely new approach to treating and preventing obesity in humans. The discovery also offers hope for new ways to treat related disorders, such as type 2 diabetes and cardiovascular diseases--the most prevalent health problems in the United States and the rest of the developed world.

Led by Dongsheng Cai, an assistant professor of physiology at the UW School of Medicine and Public Health, the researchers looked specifically at the hypothalamus--the brain structure responsible for maintaining a steady state in the body--and for the first time found that a cell-signaling pathway primarily associated with inflammation also influences the regulation of food intake. Stimulating the pathway led the animals to increase their energy consumption, while suppressing it helped them maintain normal food intake and body weight.

The research stems from recent explorations into the problem called metabolic inflammation, a by-product of too much food or energy consumption. Unlike the classical inflammation typically observed in infections, injuries and diseases such as cancer, the metabolic inflammation seen in obesity-related diseases is much milder, doesn't lead to overt symptoms or cause tissues damage.

"Metabolic inflammation is a chronic, low-grade condition consisting of inflammatory-like responses at the molecular level. It has many downstream consequences," says Cai. "It causes cellular dysfunction, which can decrease the regulation of several physiological processes, including metabolism."

Scientists believe that metabolic inflammation may be at the core of many chronic, obesity-related metabolic disorders that are so common today, he adds.

Cai and his team zeroed in on NF-kappaB, a protein complex that can be activated specifically by IKKbeta to induce inflammatory reactions in many cell systems.

In earlier studies at Harvard, Cai and colleagues found that the pathway interrupted sugar, fat or protein metabolism in tissues where metabolism typically takes place--liver, fat and skeletal muscle. Feeding mice high-sugar and high-fat diets activated the pathway in these tissues.

Once he arrived at the SMPH three years ago, Cai began to consider whether metabolic inflammation might affect "higher-up" players in the central nervous system, particularly the hypothalamus. This brain structure is a critical master regulator of appetite and energy balance, and also controls metabolism in the peripheral tissues he had studied before. But nobody knew how the hypothalamus might contribute to the development of metabolic diseases such as obesity and diabetes.

"We wanted to learn whether the pathway or pathways underlying metabolic inflammation could affect metabolism regulators in the central nervous system," he says.

In the current study, Cai and his team found first that IKKbeta/NF-

kappaB does indeed exist in specific neurons in the hypothalamus. The pathway is much more abundant in the hypothalamus than in peripheral tissue, and it normally remains inactive in the brain.

The researchers next showed that over-nutrition through high-fat diet feeding activates IKKbeta/NF-kappaB, specifically in neurons in the hypothalamus.

"When we knocked out the IKKbeta gene to suppress NF-kappaB activity in these neurons, the animals were significantly protected from energy over-consumption and obesity development," Cai says.

The researchers also examined a cell component called the endoplasmic reticulum (ER), shown recently to be involved in metabolic diseases involving over-nutrition, to see if it might play a role in linking over-nutrition to activate IKKbeta/NF-kappaB in the hypothalamus.

"At the intracellular level, when the ER is challenged with over-nutrition, this leads to ER stress, which can push the IKKbeta/NF-kappaB pathway to an active state, although the involved reactions could be quite complicated," Cai says.

In several experiments, the researchers found that ER stress caused by over-nutrition activated IKKbeta/NF-kappaB in the hypothalamus. Suppressing ER stress in the central nervous system significantly preserved normal regulation of food intake and prevented obesity.

Cai says there's still a lot of work to be done. His group has begun studying IKKbeta/NF-kappaB's connections to other pathways and regulations in the hypothalamus.

"The ultimate goal will certainly be to identify a selective and effective suppressor of the pathway to target related neurons," he says.

But Cai continues to look at the big picture, seeking answers to questions such as: "How does the environment connect to the genetics that seem to underlie the obesity epidemic? What are the key steps that have led to the dramatic rise of diabetes in the past three decades? and Why can't the body adjust to changes that have occurred in the way people eat and what they eat?"

Source: University of Wisconsin-Madison

Citation: Research team discovers brain pathway responsible for obesity (2008, October 2)
retrieved 10 April 2024 from
<https://medicalxpress.com/news/2008-10-team-brain-pathway-responsible-obesity.html>

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