System in brain -- target of class of diabetes drugs -- linked to weight gain

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University of Cincinnati (UC) researchers have determined why a certain class of diabetes drugs leads to weight gain and have found that the molecular system involved (PPAR-γ found in the brain) is also triggered by consumption of high-fat foods.

The study could lead to the modification of existing diabetes therapies and even dietary recommendations to limit the action of this nuclear receptor in the brain.

The research, led by Randy Seeley, PhD, UC professor and Donald C. Harrison Endowed Chair in Medicine, appears as an advanced online publication May 1, 2011, in the journal *Nature Medicine*.

PPAR-γ is found in white adipose (fat) tissue where it regulates the production of fat cells. This new research describes an important role for PPAR-γ in the brain.

PPAR-γ is the target of a class of diabetes drugs called TZDs (thiazolidinediones). This class of drugs reduces blood glucose levels but also causes considerable weight gain. That weight gain, Seeley says, makes many patients reluctant to use these therapies particularly since many are already trying to lose weight to improve their diabetes.

Seeley and his team set out to determine whether or not the brain's PPAR-γ system was responsible for the weight gain associated with TZDs. The team also wanted to learn if this system in the brain was

activated by a high-fat diet.

To do so, they used animal models to test how the class of drugs interacted with the brain PPAR-γ system. They found that by giving TZD drugs in the same manner that people take them, rats gained weight. This was because the drugs activated PPAR-γ in the brain. Thus, weight gain associated with this class of drugs may not be a result of action of PPAR-γ in fat as had been previously thought, but rather a result of a change in activity in parts of the brain known to regulate appetite.

Seeley's team went on to also show that high-fat diets result in activation of the brain PPAR-γ system. Experiments in which the activity of the brain PPAR-γ system was limited resulted in less weight gain when animals were exposed to a high-fat diet similar to diets of many Americans.

"If you artificially turn on PPAR-γ, you can increase food intake in rats," says Seeley. "If you block these receptors in animals on high-fat diets that make animals obese, animals gain less weight."

In the past, says Seeley, people thought that the production of more fat cells in response to TZD drugs was the cause of the resulting weight gain, but he adds, "Just having more fat cells is not enough to make animals or people fatter. Rather you have to eat more calories than you burn and that is exactly what happens when you turn on the brain PPAR-γ system.

"This work helps us understand the complex relationship between our fat, our appetites and type 2 diabetes."

Fat cells are actually quite protective and act as safe repositories for excess nutrients that cause damage when stored in other tissues like the

liver and muscle, says Seeley. "It's when nutrients are stored in these cells that individuals are at increased risk for metabolic diseases such as type 2 diabetes."

This, he says, is why TZDs are effective at lowering glucose. The extra fat cells produced become the storage containers for nutrients that would otherwise be harmful if they are stored in other areas of the body.

"You can think of your fat tissue like a bathtub," Seeley says. "A bathtub is designed to hold water. It's a good place to store it. If you turned on the faucet but didn't have a bathtub, the water would go to other parts of your house and cause water damage."

The same is true for nutrients, says Seeley. "It is better to store them in your fat tissue "bathtub" than to have them go to other parts of your body where they can do more harm."

Seeley says PPAR-γ is a system designed at all levels to help you prepare to eat more and gain weight opening up the possibility that food we eat that can activate PPAR-γ might contribute to increasing rates of obesity.

"It tells your brain to eat more and it tells your fat tissue to add new fat cells to serve as repositories to store those extra calories."

He says the next steps would be to find ways to redesign TZDs so that they retain their important glucose-lowering function but with less access to the brain, thereby limiting weight gain.

In the longer term, Seeley says, it's important to better understand the interaction between the brain's PPAR-γ system and the specific micronutrients we consume from fat, protein and sugar.

"We know that one way to activate PPAR-γ is by exposing cells to fatty

acids. If we know which ones activate PPAR-γ, we could find ways to alter diets so as to limit their ability to turn on this system that drives increased food intake, making it easier for people to avoid weight gain."

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