Scientists Identify New Mechanism of Insulin Resistance

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Resistance to insulin that precedes type 2 diabetes may stem from a "metabolic traffic jam" that blocks the body's ability to switch between glucose and fat as energy sources, say researchers at Duke University Medical Center.

Normal blood glucose (sugar) control depends on insulin, a hormone that's released after eating that stimulates sugar uptake in muscles and other parts of the body. Insulin resistance arises when the body no longer responds to insulin's signals. It's a serious condition that often accompanies obesity and increases risk of developing type 2 diabetes, a disease marked by dangerously high blood sugar levels. Scientists have been studying the disorder for years, but have not been able to agree upon its root cause.

But Debbie Muoio, an assistant professor of medicine in Duke's Sarah W. Stedman Nutrition and Metabolism Center thinks she may have a pretty good idea. She and her colleagues trace the development of insulin resistance to overworked mitochondria – the tiny power plants inside each cell – that simply get worn down and worn out trying to burn excess fat.

The study appears in the current issue of *Cell Metabolism*.

Normally, the body switches fuel sources during the day, says Muoio, a phenomenon known as "metabolic flexibility."

"For example, overnight and during periods of fasting or exercise, muscles and other organs in the body burn fat as fuel. That's because there is usually more fat available at that time. But during the day, and especially after a meal, mitochondria switch to glucose," she says. This makes sense, because food makes more glucose available and healthy individuals increase glucose use when it's on hand. But there's the hitch: If the diet is consistently too rich in fat and calories, the switchover does not occur. The mitochondria just keep working harder and harder to burn all the fat, and the effort eventually fails.

This is what leads to a "metabolic traffic jam," – a mitochondrial gridlock where fat accumulates and blocks the use, or metabolism, of glucose. Muoio believes that chronically stressed mitochondria send out a distress signal that prevents insulin from doing its job, allowing sugar to build up in the blood.

"We think this is what leads to insulin resistance," says Muoio, who acknowledges that the idea is not entirely new. "The first seeds of this hypothesis were actually planted fifty years ago, but it died out because researchers lacked the investigative tools to prove it."

Now, they have them. Muoio's team used a mass spectrometer to identify mitochondrial metabolites – by-products of fat-burning – that were found to be associated with obesity and the onset of insulin resistance.

They also developed cell and animal models that showed that when deprived of a fat-importing enzyme, mitochondria were protected and muscles continued to respond to insulin's signals, suggesting that fat overload was indeed the culprit.

There is some good news in all of this, though, says Muoio. "There are two very easy ways to prevent insulin resistance: Exercise more – you'll

help mitochondria burn fat more effectively, or eat less fat in your diet. That's always easier said than done, of course."

Several other investigators from the Stedman Center contributed to the research, including lead author Timothy Koves, Robert Noland, Dorothy Slentz, Merrie Mosedale, Olga Ilkayeva, James Bain, Robert Stevens and Christopher Newgard. Additional co-authors include Gary Lopaschuk, John Ussher and Jason Dyck, from the University of Alberta. Lopaschuk and Dyck investment in a company interested in developing inhibitors to an enzyme central to the mitochondrial activity described in the study.

Source: Duke University Medical Center