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Researchers Identify New Cause of Insulin Resistance

Howard Hughes Medical Institute researchers have tracked the cause of insulin resistance in the offspring of patients with type 2 diabetes to abnormalities in their mitochondria, the cell's "power plants."

Mitochondria are responsible for the breakdown of fatty acids. Impairment of mitochondrial function causes buildup of fats and fatty acids inside muscle that can produce insulin resistance, which, in turn, can contribute to the development of diabetes later in life.

"These new findings identify potential new targets for drugs that could either treat or prevent type 2 diabetes."

— **Gerald I. Shulman**

The researchers, led by Howard Hughes Medical Institute investigator Gerald I. Shulman, who is also professor of medicine and physiology at Yale, published their findings in the February 12, 2004, issue of the *New England Journal of Medicine*.

"Prior to this work, it was pretty clear that insulin resistance was the best predictor for the development of type 2 diabetes; and that accumulation of lipid in muscle correlated very strongly with insulin resistance," said Shulman. This correlation has been observed in cross-sectional studies, as well as in young people with a family history of type 2 diabetes, he said.

The hormone insulin promotes the transport of blood glucose into cells for energy production and storage. Mitochondria within the cells convert glucose and fatty acids into energy via oxidation. Type 2 diabetes develops when cells do not respond to insulin, causing accumulations of glucose in the blood.

To explore the metabolic origin of insulin resistance, Shulman and his colleagues recruited young healthy volunteers who tested positive for insulin resistance and who were the offspring of patients with type 2 diabetes. They also recruited a second, control group of volunteers who exhibited insulin sensitivity who were matched for age, height, weight and physical activity.

“These subjects are ideal candidates for studies examining the earliest defects leading to insulin resistance, since in contrast to patients with diabetes, they are young, lean, healthy, and unlikely to have other confounding factors that might cause insulin resistance,” the authors wrote in the *New England Journal of Medicine*.

Further analysis using a technique called proton magnetic resonance (MR) spectroscopy confirmed that the muscle cells of the insulin-resistant subjects did, indeed, harbor higher levels of fat. Previous studies by Shulman and his colleagues had shown that intramuscular fat interferes with molecular pathways within the cell that enable insulin action. In MR spectroscopy, harmless magnetic fields and radio frequency pulses are used to detect and quantify signals characteristic of specific molecules.

According to Shulman, the researchers had to distinguish between two possible causes of the fat accumulation in the muscle that could trigger insulin resistance. “Either there were defects in the fat cells, called adipocytes, in which there was increased release of fatty acids to muscle cells,” said Shulman. “And/or, there was a defect in mitochondrial function in the muscle cells which would lead to decreased metabolism of these fatty acids. So, we designed the study to look at both of these possibilities.”

The researchers then performed metabolic and tracer studies which could reveal in detail whether the insulin-resistant offspring of patients with diabetes had defects in lipid metabolism, or lipolysis, that could explain their insulin resistance.

“We found that these lean insulin-resistant offspring—who have a high probability of later developing type 2 diabetes—had muscle insulin resistance, but no detectable abnormalities in their fat cells compared to the insulin-sensitive subjects,” said Shulman.

The researchers then turned their attention to the mitochondria within the cells of the insulin-resistant offspring, using a technique called phosphorus magnetic resonance spectroscopy. This technique can reveal how well the energy-producing machinery of the mitochondria is functioning to break down fat, to produce the cell's chief energy carrying molecule, phosphorus-rich ATP.

“Using this method we found that rates of ATP production in the muscles of the insulin-resistant offspring was decreased by thirty percent compared to normal subjects,” said Shulman. Further phosphorous MR spectroscopy studies revealed a reduction in the ratio of slow-twitch (oxidative) muscle fiber type compared to fast-twitch (glycolytic) muscle fiber type in the insulin-resistant offspring. These data suggest that there may be an inherited gene that leads to fewer mitochondria in the muscle of insulin-resistant offspring, resulting in slightly lower rates of fatty acid oxidation” he said.

Shulman and his colleagues are now performing muscle biopsy studies to determine whether the mitochondrial impairments are due to defects in the mitochondria themselves, or due to a reduced number of mitochondria in the

subjects' cells.

“The other direction of our research is to discover whether or not we can reverse these abnormalities with exercise,” said Shulman. “It is pretty well established that training will increase mitochondrial content. For example, it is well known that marathon runners have more mitochondria than sprinters.” Earlier studies by Shulman's group established that exercise could promote activation of an enzyme called AMP kinase that can lead to an increase in mitochondria content.

“These new findings identify potential new targets for drugs that could either treat or prevent type 2 diabetes. Furthermore, these data may help guide us to a better understanding of the genetic basis of type 2 diabetes”, said Shulman.