

AUGUST 15, 2005

Type 2 Diabetes: Problems in the Furnace

A detectable decline in energy production by mitochondria—the organelles that are the cell's furnace for energy production—seems to be a key problem leading to insulin resistance, and thus to type 2 diabetes, according to studies by Howard Hughes Medical Institute researchers.

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— **Gerald I. Shulman**

The research team said that insulin resistance—an impaired response to the presence of insulin—is detectable as early as 20 years before the symptoms of diabetes become evident. In fact, insulin resistance is now seen as the best predictor that type 2 diabetes will eventually develop, said the study's senior author, Gerald I. Shulman, a Howard Hughes Medical Institute investigator at the Yale University School of Medicine.

In the new study examining how insulin interacts with the energy-producing mitochondria inside living cells, Shulman and his colleagues found that the rate of insulin-stimulated energy production by mitochondria is significantly reduced in the muscles of lean, healthy young adults who have already developed insulin resistance and who are at increased risk of developing diabetes later in life.

“This is further evidence that people who are prone to develop diabetes have signs of mitochondrial dysfunction,” Shulman said in an interview. This is important because mitochondria are the “energy factories” inside cells and produce most of the chemical power needed to sustain life.

The new research, which is published in the September 2005 issue of the open-access journal *PLoS Medicine*, indicates that a decreased ability to burn sugars and fats efficiently is an early and central part of the diabetes problem. Their new data also suggest the basic defect lies within the mitochondria, which exist in almost every cell.

The young adults studied by the research team are the offspring of parents who have type 2 diabetes, adding support to the idea that the risk can be inherited, and that the problem begins well before diabetes symptoms become evident. In an earlier research study published in the journal *Science*, Shulman and his colleagues had also found that healthy, lean older individuals have a major reduction in mitochondrial energy production that leads to accumulation of fat inside muscle cells resulting in insulin resistance. “These data may explain the increased prevalence of type 2 diabetes that occurs with aging” Shulman said.

In the new studies, Shulman and his Yale colleagues—Kitt Falk Petersen and Sylvie Dufour—discovered that the mitochondria in muscle cells respond poorly to insulin stimulation. Normal mitochondria react to insulin by boosting production of an energy-carrying molecule, ATP, by 90 percent. But the mitochondria from the insulin-resistant people they tested only boosted ATP production by 5 percent.

“These data demonstrate that insulin-stimulated rates of ATP synthesis are reduced in the insulin-resistant offspring of parents with Type 2 diabetes,” the researchers wrote in their report. Their work offers new insight into the early steps in the development of insulin resistance, and offers important clues to where the problem lies.

Among their findings was also evidence for a severe reduction in the amount of insulin stimulated phosphorus transport into the muscle cells of the insulin-resistant participants. This also points to a dramatic defect in insulin signaling and may explain the observed abnormalities in insulin-stimulated power production in the insulin-resistant study subjects, since phosphorus is a key element in the mitochondrion's complex energy-production process, the oxidative-phosphorylation pathway.

“Type 2 diabetes affects about 171 million people worldwide, and the number of people likely to be affected by diabetes is expected to double by 2030,” Shulman and his colleagues added. “Type 2 Diabetes develops when resistance to insulin action is combined with impaired insulin secretion,” resulting in a severe oversupply of sugars and fats in the blood. “Studies have demonstrated the presence of insulin resistance in virtually all patients with type 2 diabetes,” Shulman added. Diabetes is the leading cause of blindness, end stage kidney disease and non-traumatic loss of limb, and has associated health care costs that exceed \$130 billion a year in the United States.

Such fundamental research is important because the problem of diabetes is growing rapidly worldwide, and effective drugs are needed to halt or even reverse the disease process. Understanding how the cell's internal energy system is controlled by the hormone, insulin, and how the mitochondria behave, may eventually lead to improved ways to overcome or prevent diabetes.