Study points to potential new drug for type 2 diabetes

March 15 2010, by Emily Caldwell

An experimental oral drug has lowered blood sugar levels and inflammation in mice with Type 2 diabetes, suggesting that the medication could someday be added to the arsenal of drugs used by millions of Americans with this disease, according to new research.

The drug consists of a synthetic molecule that stops the biological activity of a protein called macrophage migration inhibitory factor, or MIF. This protein is implicated in a number of diseases because it is associated with the production of inflammation in the body.

The researchers first determined that mice that have been genetically engineered not to carry the MIF protein are less likely to develop symptoms of Type 2 diabetes. This finding suggested that MIF indeed has a role in at least two hallmarks of diabetes: impaired blood sugar control and the presence of other inflammatory proteins.

The scientists then treated diabetic mice with the investigational drug and found that most animals showed lower blood sugar levels and reduced inflammatory proteins in their blood when compared to untreated mice with Type 2 diabetes.

"We also found that if we stopped administering the drug, then the blood sugar level would go up," said Abhay Satoskar, associate professor of pathology at Ohio State University and senior author of the study. "This does not present a cure for diabetes, but we think, if it is approved in humans, that it has potential to become an oral drug taken for the long

term to control a very common symptom of the disease."

The researchers supported their animal findings by measuring proteins and hormones in blood samples from a small group of people with Type 2 diabetes and healthy human participants for comparison. The patients with diabetes had significantly higher levels of MIF in their blood than did the healthy patients, as well as higher levels of two compounds that contribute to inflammation and insulin resistance.

"All of this evidence combined suggests strongly that MIF is a viable therapeutic target in Type 2 diabetes," Satoskar said.

The study appears online and is scheduled for later print publication in the *Journal of the Federation of American Societies for Experimental Biology*.

This research applies only to non-insulin-dependent diabetes mellitus and not Type 1 diabetes, which occurs when the pancreas does not produce enough insulin. Not all people with Type 2 diabetes have a shortage of insulin, but their bodies do not respond correctly to the hormone.

Insulin is responsible for transferring sugar, or glucose, from the blood into the cells to be used for energy. When people become insulin resistant, the main characteristic of Type 2 diabetes, that process does not function properly, which tends to drive up blood sugar levels and starve cells of energy.

Many current diabetes drugs stimulate the body to release more insulin or otherwise act in a way that affects sensitivity to insulin. A drug targeting MIF could offer different benefits by lowering blood sugar and inflammation without the need to generate more insulin, Satoskar noted.

Satoskar and colleagues induced Type 2 diabetes in two groups of mice: normal mice and those lacking MIF. They induced the disease by injecting them one time with a naturally occurring toxin, streptozotocin, which acts on cells in the pancreas.

Researchers collected blood samples from the mice multiple times over 10 weeks, conducted oral glucose tolerance tests, and monitored their weight and urine output.

All animals with induced disease showed a spike in blood sugar levels shortly after the injection of the toxin, but the blood sugar levels continued to rise in the normal diabetic mice. These mice also took in more food, lost weight and produced excessive amounts of urine - all symptoms associated with insulin resistance.

Mice lacking the MIF protein, on the other hand, showed a drop in their blood sugar levels by week seven and experienced minimal weight loss. Additionally, after glucose tolerance tests, the blood sugar levels in mice lacking MIF decreased more rapidly than did levels in normal diabetic mice.

Finally, the mice lacking MIF produced significantly lower amounts than the normal mice of two proinflammatory cytokines: interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). These are chemical messengers that cause inflammation, most often to fight infection or repair injury. When these proteins circulate without an infection to fight, the body experiences excess inflammation, which is associated with a variety of diseases depending on which cells are producing the proteins.

All of these observations led researchers to believe that MIF has one or more roles in the development and maintenance of Type 2 diabetes, Satoskar said.

The researchers next induced Type 2 diabetes in a different group of normal mice. Five days after the disease was induced, the scientists treated the animals daily for 30 days with the investigational drug, called CPSI-1306 by its manufacturer, Cytokine PharmaSciences Inc. Two doses of the drug, one dose 10 times stronger than the other based on body weight, were put in water and given to the mice by mouth.

After four weeks of treatment, the mice receiving both levels of the drug sustained blood sugar levels of below 200 milligrams per deciliter. Experts suggest that blood glucose after eating should remain below 180 milligrams per deciliter in people with diabetes. By comparison, the blood sugar levels in untreated diabetic mice exceeded 400 milligrams per deciliter.

"The blood sugar levels came down to very near normal in the treated mice," Satoskar said.

Similarly, levels of IL-6 and TNF-alpha were substantially lower in treated mice vs. untreated mice. Animals receiving the higher dose of the drug, 0.1 milligram per kilogram of body weight, showed the lowest levels of these proinflammatory cytokines.

Satoskar explained that the molecule in the drug binds to MIF in a way that allows it to strip MIF of its three-part structure, preventing MIF from become biologically active. MIF is always present in the body, but isn't considered problematic until excess amounts of it are produced and active. Though it might have some physiological role in normal amounts, blocking it or interfering with its activity does not appear to cause any side effects in animals, he said.

The researchers suspect MIF acts on adipocytes, the cells that make up fat tissue, because they also found that the mice lacking MIF showed significantly lower levels than normal diabetic mice of a hormone called

resistin, which is produced by adipocytes and contributes to insulin resistance.

"Finding that mice without MIF have less resistin suggests that MIF might do its damage by acting on adipocytes and making them produce more inflammation," Satoskar said.

Because Type 2 diabetes is strongly associated with obesity, these cells also could be responsible for production of the inflammatory cytokines that were shown in this study to be elevated in mice and humans, he said.

He and colleagues next plan to test the investigational drug on mice that model obesity and typically develop Type 2 diabetes after eating a high-fat diet.

Provided by The Ohio State University