

New link between obesity and diabetes found

November 21 2013

A single overactive enzyme worsens the two core defects of diabetes—impaired insulin sensitivity and overproduction of glucose—suggesting that a drug targeting the enzyme could help correct both at once, according to mouse studies done by researchers at Columbia University Medical Center. The findings were published today in the online edition of *Cell Metabolism*.

A [drug](#) that inhibits the enzyme, MK2, eventually could be added to metformin—the current first-line treatment for type 2 diabetes—to achieve better control over insulin and [glucose levels](#) than is possible with either drug alone, said the researchers.

"MK2's compatibility with metformin makes it a very exciting potential drug target," said Ira Tabas, MD, PhD, Richard J. Stock Professor and Vice Chair of Research in the Department of Medicine and professor of anatomy & cell biology (in physiology and cellular biophysics), who led the study with Lale Ozcan, PhD, associate research scientist.

"The one clear leader among drugs currently available for type 2 diabetes is metformin, which does a pretty good job of attacking both problems. But because metformin is often not enough, we need drugs that can be added to metformin—or used in patients who cannot tolerate metformin," Dr. Tabas said. "If you take an obese, diabetic mouse and give it metformin, you get a partial improvement. If you give it an MK2-inhibitor, you also get a partial improvement. However, if you give both, the benefit is additive, which is consistent with our data that metformin and MK2 work through different biochemical pathways."

The researchers' earlier findings, on MK2's effects on glucose, were published last year in the same journal.

Though both papers report the biochemical details of how MK2 works in mice, Drs. Tabas and Ozcan, working with CUMC surgeons Marc Bessler, MD, and Beth Schrope, MD, PhD, also have recent unpublished data suggesting that MK2 is overactive in obese people, including those with pre-diabetes, but not in lean people. Moreover, the MK2 pathway is active in human liver cells, and, according to a large human genetic study called DIAGRAM, a key component of the pathway that activates MK2 is associated with diabetes.

About 25.8 million people in the U.S. and 347 people worldwide have diabetes (mostly type 2). According to the Centers for Disease Control and Prevention, each year, about 6 percent of people with pre-diabetes develop [type 2 diabetes](#); unless they make lifestyle changes, about 15 to 30 percent will develop diabetes within five years. "In addition to improving [insulin sensitivity](#) and glucose levels, our data suggest to us that a drug that inhibits MK2 could prevent the progression of pre-diabetes to full diabetes," Dr. Tabas said.

Such a drug could protect the cells that produce insulin. "As the disease progresses, the insulin-producing cells have to put out more and more insulin to deal with the ever-increasing amounts of glucose in the bloodstream. Eventually, they burn out and the patient must use insulin," Dr. Tabas said. "If we can protect the pancreas's beta cells from the stress of dealing with high glucose, we may be able to prevent or delay progression to full diabetes."

Drs. Tabas and Ozcan are planning to test this hypothesis with pre-diabetic mice.

Inhibiting MK2 also reduces cholesterol

Unpublished data from Drs. Tabas and Ozcan also suggest that MK2 inhibitors may not carry the cardiovascular risks associated with several newer diabetes drugs. Because of these risks, the FDA will not approve a new diabetes drug unless it has been found to be safe in large clinical trials designed to detect cardiovascular risk.

The Columbia researchers' mouse studies show that MK2 inhibition reduces cholesterol, and other researchers have found that MK2 deficiency in mice protects against atherosclerosis. "A drug that inhibits MK2 may not just be heart-safe, but may actually be cardio-protective," Dr. Tabas said.

He and Dr. Ozcan have created a company to develop compounds able to inhibit MK2.

"As with all drug development, it's a long shot, but we think MK2 is less of a long shot than most."

Drs. Tabas' and Ozcan's paper is titled, "Activation of Calcium/Calmodulin-Dependent Protein Kinase II in Obesity Mediates Suppression of Hepatic Insulin Signaling."

Provided by Columbia University Medical Center

Citation: New link between obesity and diabetes found (2013, November 21) retrieved 9 April 2024 from <https://medicalxpress.com/news/2013-11-link-obesity-diabetes.html>

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