

Protein target for diabetes drug regulates blood pressure

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University of Iowa researchers have identified a molecular pathway in blood vessels that controls blood pressure and vascular function and may help explain why certain drugs for type II diabetes also appear to lower patients' blood pressure. The study is published in the March 5 issue of *Cell Metabolism*.

A majority of patients with type II diabetes, which is associated with obesity and metabolic syndrome, also are at risk for serious cardiovascular problems, including atherosclerosis, heart attack, stroke and hypertension. Understanding the biological pathways that link cardiovascular and metabolic function could lead to better treatments for the millions of Americans affected by these conditions.

The focus of the UI study is a protein called peroxisome proliferator-activated receptor gamma (PPAR gamma), which plays a critical role in fat metabolism and insulin action, and appears to link metabolic disorders, like type II diabetes, with cardiovascular disease.

Drugs called thiazolidinediones (TDZs), which are used to treat type II diabetes, target and activate PPAR gamma. In addition to controlling blood sugar, these drugs also appear to lower blood pressure.

The UI team led by Curt Sigmund, Ph.D., professor of internal medicine and molecular physiology and biophysics in the UI Roy J. and Lucille A. Carver College of Medicine, and Carmen Halabi, a student in the UI Medical Scientist Training Program and the study's lead author, tested

the idea that these two beneficial effects of TZDs are produced through two separate PPAR gamma pathways.

Working with mice, the team knocked out the function of PPAR gamma in vascular smooth muscle, which surrounds blood vessels. The mice developed high blood pressure and very severe vascular dysfunction, which resembled the vascular disorders often seen in patients with advanced type II diabetes.

"It appears that when PPAR gamma is activated it initiates a cascade of events that protect the blood vessel," Sigmund explained. "When we interfere with the PPAR gamma pathway, those protective mechanisms are eliminated and the blood vessel becomes dysfunctional."

Although TZDs have been used for many years to treat type II diabetes, they do have several serious side effects, including weight gain and water retention. A recent study also suggested that one TZD (rosiglitazone, which is sold as Avandia) might increase the incidence of fatal and non-fatal heart attacks in diabetes patients. Avandia now carries an FDA warning.

"These side effects really highlight the need to figure out ways to dissociate beneficial effects from dangerous side effects," Sigmund said. "By understanding the mechanisms that lead to those effects we may be able to enhance benefits and minimize dangers."

"When a drug is found to have serious side effects, people often think that the molecule the drug targets is no longer relevant," he added. "But that is not the case. We know from our study and from others that the molecule is still very relevant. We just need drugs with higher specificity."

Sigmund also noted that Halabi's combined training in medicine and

bench science helped to focus the genetic study on an area with direct clinical relevance.

"This study is at the interface of her knowledge of clinical medicine and the basic science," he said.

PPAR gamma is a transcription factor and when it is activated, a cascade of signals is initiated, which controls gene expression -- some genes are turned on and others are turned off. In particular, inflammatory genes are turned off and antioxidant genes are turned on.

Having identified the PPAR gamma pathway, the next question for the researchers is which genes are being turned on or off to produce the antihypertensive effect" Identifying these genes may lead to more specific ways of treating hypertension and vascular disease in patients with diabetes.

Source: University of Iowa

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