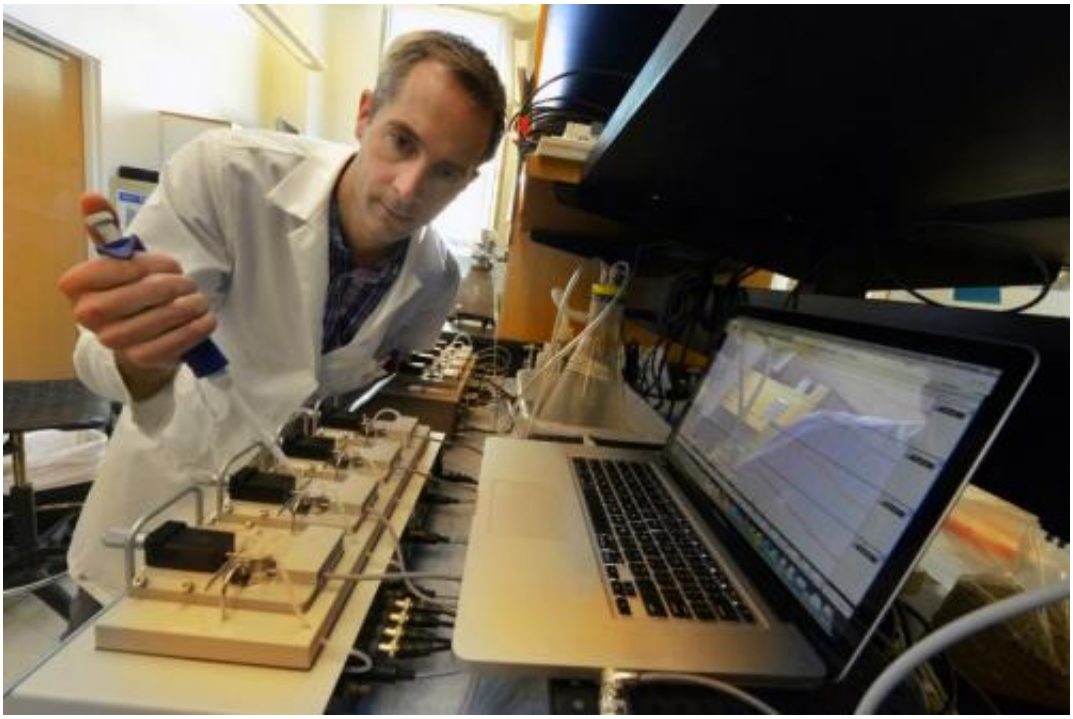
Researcher works to block the blood-vessel dysfunction that occurs in diabetes

December 3 2014



One of diabetes' dangerous consequences is dysfunction of the single-cell layer that lines our blood vessels. Credit: Phil Jones, Georgia Regents University

One of diabetes' dangerous consequences is dysfunction of the single-cell layer that lines our blood vessels.

Too much circulating sugar and fat can leave our endothelial lining inflamed and unable to dilate properly, driving blood pressure up, which

multiplies the problem and sets the stage for vascular disease, said Dr. Eric Belin de Chantemele, physiologist at the Medical College of Georgia at Georgia Regents University.

Now researchers suspect a protein, which is already a hot therapeutic target for the prevention of obesity and diabetes, may be one as well for the disabling and potentially deadly endothelial dysfunction.

A new one-year, $100,000 grant from the Diabetic Complications Consortium of the National Institute of Diabetes and Digestive and Kidney Diseases is funding a study of human arteries and veins removed during heart surgery to help determine if they're right.

A major factor in the vascular dysfunction that can result from diabetes as well as obesity and hypertension, is reduced production of nitric oxide by the endothelial cells that line blood vessels. This short-lived gas, which is also produced by automobiles and plants, is the body's most powerful blood vessel dilator, enabling the 60,000-mile vasculature to dilate, instantaneously enabling increased blood flow.

Nitric oxide also decreases excretion of cytokines, immune cells that promote inflammation, so less of it means increased blood flow turbulence, which promotes cytokine secretion, so - rather than just attacking invaders such as bacteria - larger numbers of the immune cells attack the blood vessel lining, helping lay a solid foundation for vascular disease.

That's why blocking PTP1B may help, Belin de Chantemele said. It's known that PTP1B expression is increased in the fat, muscle, and livers of people with diabetes. MCG scientists were looking at the effect of PTP1B on the whole body when they noted that mice missing it had higher blood pressure but not the endothelial dysfunction they would expect. They also found that when they induced type 1 diabetes in mice

missing the protein, the mice also didn't experience endothelial dysfunction.

"We know that diabetes increases PTP1B expression in all those tissues, the muscle, the liver, fat, and what we want to see now is if diabetes also increases PTP1B in endothelial cells and if that increased expression leads to the endothelial dysfunction," Belin de Chantemele said.

With the help of segments of human saphenous veins, used to bypass diseased coronary arteries, and tiny aortic puncture biopsies, taken from where the bypasses are placed by MCG Cardiovascular Surgeon Dr. Vijay Patel, the scientist is looking for the first time at PTP1B expression in the endothelial cells of patients with diabetes versus those without it. He's also measuring markers of a stressed out endoplasmic reticulum, or ER, a fundamental organelle inside those cells.

The ER helps ensure cells contain proper levels of calcium, which is essential to cell function, and controls protein folding, which is essential to protein function. In the case of the protein PTP1B, it appears to be a reciprocal relationship, because Belin de Chantemele thinks PTP1B may regulate ER function.

Much like the rest of the body, the ER is stressed by the high blood glucose levels of diabetes. While endothelial cells have mechanisms to protect this important organelle, the sustained activation that occurs in diabetes can instead prompt cell death: too much of a good thing ends up being lethal rather than protective to endothelial cells and probably other cell types. "It could just be a consequence, but we really think it's a player," Belin de Chantemele said. In fact, it's already known that diabetics have increased ER stress, but the PTP1B connection is new.

MCG scientists are finding when they remove PTP1B from this scenario, at least in their animal model, it improves ER function and cell

survival. "The cells are still viable," Belin de Chantemele said. "We probably are often exposed to ER stress, but our system is able to cope with it. You eat candy, you have too much glucose, and you will stimulate endoplasmic reticulum stress, but your cells are in good shape and can fix themselves. But if they are chronically stimulated and stressed, the cells will not be able to fix themselves, and they will die."

Drug companies are having trouble developing PTP1B inhibitors because of side effects from blocking the multipurpose protein. Belin de Chantemele hopes his lab's additional findings about the roles of PTP1B will aid development of a more targeted inhibitor.

The protein's laundry list of functions includes controlling the body's sensitivity to insulin and leptin - known as the satiety hormone. Although inhibitors cause the body to make less of both, it becomes more sensitive to both. As an example, PTP1B blocks the action of insulin, which basically tells your fat, liver, and muscle to take up circulating glucose so it can be used for energy later. When that doesn't happen as it should, high glucose levels circulating throughout the body damage cells. That's why PTP1B inhibitors likely will be effective with weight loss and diabetes: people will take up more glucose and have more energy. "If you have more leptin secretion and your brain is less sensitive, you will continue to eat and become more obese," Belin de Chantemele said.

Provided by Medical College of Georgia