Insulin plus growth factor inhibitor limits vision damage in diabetic mice

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A new therapeutic approach to diabetes that combines insulin and an inhibitor of the epidermal growth factor (EGF) betacellulin could limit the progression of diabetic macular edema (DME), Cleveland Clinic researcher Bela Anand-Apte, MD, PhD, said at the American Society for Cell Biology Annual Meeting, on Dec. 17 in San Francisco.

The study, conducted with insulin-dependent diabetic mice, showed that by thwarting "cross-talk" between insulin and betacellulin (BTC), which promotes the regeneration of pancreatic beta cells that stores and releases insulin, the EGF inhibitor preserved the animals' vascular integrity, she explained.

"These studies suggest that a combinatorial treatment of insulin and EGF inhibition might be a useful therapeutic combination to prevent macular edema, but needs to be determined in people with diabetes," said Dr. Anand-Apte.

Dr. Anand-Apte's idea for disconnecting diabetic progression from retinopathy was suggested by studies in people with type II diabetes whose blood sugar control was no longer stable on oral medications, requiring them to be treated with insulin. She noted that insulin therapy appeared to result in some patients' retinopathy progressing much faster, at least for a time. There was a correlation between starting insulin therapy and developing DME, she said.

Another clue came from an observation made by Judah Folkman, MD,

then at Boston Children's Hospital, about pancreatic cancer patients who had undergone a pancreatectomy. Without a pancreas to produce and regulate insulin, these patients developed severe diabetes but rarely if ever developed proliferative retinopathy, even when they survived for more than 10 to 20 years. In the pancreas of people with diabetes, the researchers hypothesized that "cross-talk" occurred between injected insulin and the secretion of a vascular permeability-inducing factor.

Working with collaborators at Case Western Reserve University and the University of Wisconsin, the Anand-Apte lab used a mouse model for diabetes to look at BTC produced in the pancreas by proliferating beta cells. In previous studies, Dr. Anand-Apte had linked BTC to increased vascular permeability in the retina. Treating diabetic mice with insulin produced a spike in levels of a soluble form of betacellulin in the retina. Simply injecting BTC into the vitreous fluid of both hyperglycemic and normal mice also increased vascular permeability.

Looking more closely, the researchers determined that insulin was disrupting tight junctions between retinal pigment cells (RPEs), the barrier layer wrapped around retinal nerves, by driving up BTC expression. Injecting insulin first increased the production of ADAM10, a protein that weakens molecular cell-cell glues. The increase in ADAM10 was followed by up-regulation of BTC. By blocking the production of BTC and ADAM10 with short interfering RNA (siRNA), the researchers discovered they could protect these cell-cell tight junctions.

Substituting a BTC-targeted EGF inhibitor, the researchers finally thwarted the cross-talk between BTC and insulin. The EGF inhibitor preserved vascular integrity in the diabetic mice.

The association of visual impairment and the progression of both type I and type II diabetes appears to strengthen over time. The National

Diabetes Information Clearinghouse estimates that of the 25.8 million American who have diabetes, 4.2 million have diabetic retinopathy, and in 675,000 of them, it progresses to its most severe form, proliferative diabetic retinopathy in which abnormal—and leaky blood vessels intrude into the eyeball's clear vitreous gel, causing retinal traction and bleeding that results in decreased sight.

Many people with diabetes with proliferative retinopathy also develop DME, a thickening of the center of the retina. Increased vascular permeability in the blood-retinal barrier allows leakage of lipoproteins into the macula at the center of the retina, reducing sharp vision. The main risk factors for DME, according to the American Academy of Ophthalmology, are increasing duration of diabetes, high blood sugar and blood pressure. Over 10 years, 20% of patients diagnosed with early-onset diabetes and 40% with older-onset diabetes will develop DME.

More information: "Regulation of retinal vascular leakage by insulin: Implications for patients with diabetic retinopathy," Monday, Dec.17, 2012, 12:30-2 pm, Session: Cell-Cell Junctions II, presentation 1351, poster B927, Exhibit Halls A-C

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