Protein critical for insulin secretion may be contributor to diabetes

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A cellular protein from a family involved in several human diseases is crucial for the proper production and release of insulin, new research has found, suggesting that the protein might play a role in diabetes.

Mice lacking the ClC-3 channel, a passageway that allows negatively-charged chloride ions to pass through cell membranes, have only one-fifth the circulating insulin of normal mice, according to research published this month in the journal *Cell Metabolism*.

Researchers Deborah Nelson and Louis Philipson of the University of Chicago, senior authors on the paper, argue that the finding may explain a portion of what goes wrong in Type 2 diabetes and could help doctors find rare patients whose diabetes has a previously-undetected genetic origin.

"Chloride regulation is not really well understood, but it's at the heart of cystic fibrosis, and it is related to the regulation of how insulin gets made," said Philipson, professor of medicine and medical director of the Kovler Diabetes Center at the University of Chicago. "Now we see that it's a critical feature of how insulin gets converted from a precursor form to its most active form."

Insulin is made and released by specialized pancreas cells called Beta-cells. The cell first synthesizes a protein called pro-insulin, discovered forty years ago at the University of Chicago by Donald Steiner, which is then put inside structures called secretory granules.

Inside the secretory granule, proinsulin is chemically converted into insulin, and the granule moves to the cell surface where it can release insulin into the blood. Steiner discovered that the conversion of proinsulin to insulin must happen in an acidic environment, but how the granules make themselves acidic was unknown.

A team lead by Ludmila Deriy, a research assistant professor in Nelson's laboratory, studied genetic knockout mice missing the ClC-3 chloride channel. The blood of those mice contained lower levels of insulin and cellular measurements discovered that fewer granules were released by Beta-cells from ClC-3 knockouts and that the granules of ClC-3 knockout mice were less acidic than those from normal mice.

High-powered electron microscope images allowed researchers to observe that the granules of ClC-3 knockout mice contained higher amounts of proinsulin than granules from normal mice. Missing ClC-3 therefore appears to cause a dramatic slowdown of the conversion of proinsulin to insulin inside the granules, said Nelson, professor of neurobiology at the University of Chicago.

"Not only is release down, but what is released is not as efficacious a molecule," Nelson said. "It's pro-insulin rather insulin, if anything's released at all."

A mutation in the function of ClC-3 in humans could very well be the cause of a select few cases of juvenile diabetes, Nelson and Philipson said. However, while other ClC proteins have been linked to bone, muscle and kidney disease, no human case of diabetes has yet been linked to the function of this specific protein. Because ClC-3 knockout mice also experience epileptic seizures, a patient diagnosed with both epilepsy and diabetes could potentially have an undetected defect in their ClC-3 channel.

"If it happens that there's epilepsy and diabetes, it's not currently recognized as a syndrome," Philipson said. "We would be extremely interested in cases like that."

Finding a patient with this rare form of genetically-caused diabetes could be aided by efforts such as Lilly's Law, an Illinois legislation signed in August that created a statewide diabetes registry. The law requires that doctors report all diagnoses of children younger than 12 months to the state Department of Public Health. Scientists can then test those children to see if their disease is caused by a genetic mutation, knowledge that can improve the child's treatment.

The law is named for Lilly Jaffe, a girl diagnosed with Type 1 diabetes that was treated by Philipson and University of Chicago Medical Center colleagues in 2006. Lilly was found to have a rare genetic mutation in a different cellular protein, meaning her disease was treatable with oral medication rather than insulin injections.

A mutation of the ClC-3 channel would probably still be treated with insulin rather than an oral medication. But observing ClC-3 function in humans may provide insight into Type 2 diabetes as well, Philipson said, as the disruption of insulin production and secretion resembles cellular effects seen in adult-onset diabetes.

"We know that Type 2 diabetes is a progressive illness where insulin secretion is high and then goes down over time, but why does it do that? This ties some connection between chloride channels and granular function to the ability of insulin to come out of the cell," Philipson said. "This could be an important pathway in Type 2 diabetes, so it's not just the rare patient that's affected, it's 25 million people in the United States."

More information: The study, "The Granular Chloride Channel ClC-3 Is

Permissive for Insulin Secretion," was published in the journal Cell Metabolism on October 7.

Source: University of Chicago (news : web)