Medical Xpress

AAT protein restores blood glucose in type 1 diabetes model

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A protein made by the liver in response to inflammation and used to treat patients suffering from a genetic form of emphysema has been shown to restore blood glucose levels in a mouse model of Type 1 diabetes mellitus, according to a new study led by researchers at Beth Israel Deaconess Medical Center (BIDMC).

The findings, which appear in the Online Early Edition of the *Proceedings of the National Academy of Sciences* (PNAS) this week, provide further proof that inflammation plays a key role in the development of Type 1 diabetes and suggest that the protein – known as AAT --might be an option for clinical testing in humans.

Formerly known as juvenile-onset or insulin-dependent diabetes, Type 1 diabetes is an autoimmune disease that develops when the body's immune cells (known as T-cells) overreact and attack and destroy its own pancreatic beta cells. Without beta cells, the body is unable to produce insulin, a hormone needed to convert glucose into energy. To prevent the development of serious – and even fatal -- complications, more than 21 million individuals with Type 1 diabetes, primarily children and young adults, must receive as many as three insulin injections each day.

"To cure Type 1 diabetes, it will not be enough to halt the destructive T-cell-dependent autoimmune attack on beta cells," explains the study's lead author Maria Koulmanda, PhD, Director of Non-Human Primate Research in the Transplant Center at Beth Israel Deaconess Medical

Center (BIDMC) and Associate Professor of Surgery at Harvard Medical School (HMS). "We think that it will also be necessary to restore proper insulin signaling, and the way to do that is by eliminating the curious inflammatory state that exists in muscle, fat and other insulin-sensitive tissues."

Last year, Koulmanda, together with the paper's senior author Terry Strom, MD, Director of Transplant Research at BIDMC and Professor of Medicine at HMS, established a role for insulin resistance and inflammation in the onset of Type 1 diabetes, a finding that challenged many theories regarding the autoimmune disease. Their findings demonstrated for the first time that a form of inflammation in fat and muscle was preventing insulin from "allowing" blood glucose into tissues requiring glucose. They further demonstrated that normal blood glucose levels could be successfully restored in a non-obese diabetic (NOD) mouse model by administering a triple combination therapy consisting of both tolerance-inducing and anti-inflammatory properties.

In this new paper, Koulmanda borrowed the AAT protein to achieve the same results.

"The AAT protein is made by the liver and functions to halt unchecked inflammation," she explains. "In cases of Type 1 diabetes, inflammation is the factor that determines whether T-cells exert destructive or protective forms of immunity. We, therefore, hypothesized that [in cases of Type 1 diabetes] immune tolerance could be reestablished by using the AAT protein to modify a pro-inflammatory state and turn it into an anti-inflammatory state."

Using the NOD mouse model, the authors tested the hypothesis that inflammatory mechanisms directly trigger insulitis, insulin resistance, faulty insulin signaling and the loss of immune tolerance to islets.

"We were able to demonstrate that treatment with AAT – an agent that dampens inflammation but does not directly inhibit T-cell activation – ablates invasive insulitis and restores euglycemia [normal blood glucose concentration], immune tolerance to beta cells, normal insulin signaling and insulin responsiveness in NOD mice with recent onset Type 1 diabetes," she says.

Most dramatic, adds Koulmanda, their experiments found that the functional mass of beta cells actually expanded in the NOD mice treated with AAT.

The AAT protein is already in widespread use as a replacement therapy in treating Alpha-1 antitrypsin deficiency, an inherited disorder that can cause emphysema-like lung disease in adults and liver disease in children.

"In humans, AAT has been used for more than two decades, and has maintained an impressive safety record," says Koulmanda. "We believe that treatment with AAT will prevent and delay further loss of functioning residual beta cells in patients with recent onset Type 1 diabetes.

"With this study, we've shown that modifications in inflammation indirectly – but powerfully – modify ongoing destructive-type immunity," she adds. "And most exciting, by administering AAT to the diabetic mice, we actually achieved beta cell expansion, which has never been shown with any other treatment."

Source: Beth Israel Deaconess Medical Center

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