

# Nervous system appears to play key role in developing Type 1 diabetes: study

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TORONTO (CP) - It's long been accepted wisdom that Type 1 diabetes occurs after a severe miscue by the immune system causes insulin-producing cells in the pancreas to be destroyed. Now Canadian-led research suggests immune cells aren't the only culprits in developing the disease - the nervous system also plays a pivotal role.

With Type 1 diabetes, the destruction of the islet cells in the pancreas leaves the body without insulin to regulate the metabolism of blood glucose, or sugar. The disease, which affects about 200,000 Canadians, can lead to severe complications even with daily insulin injections, including blindness, limb amputation and kidney failure.

In studies of laboratory mice specially bred to make them susceptible to Type 1 diabetes, researchers at the Hospital for Sick Children and the University of Calgary discovered that a control circuit exists between insulin-producing cells and their associated sensory, or pain-related, nerves.

It turns out that this control circuit is necessary to retain the health and normal function of islet cells, said principal investigator Dr. Michael Dosch, an immunologist at Sick Kids Hospital.

"What we really have discovered is that the immune system is under much closer control by the nervous system than we thought, that this control to a large extent involves sensory nerves," said Dosch, explaining that such nerves are the same kind that signal the brain to send out pain messages when an ankle is broken or a finger is burned on a hot stove.

As part of their studies, the scientists knocked out specific pain-related nerve cells in newborn lab mice. These nerve cells secrete a chemical called "substance P," which is known to amplify pain signals as well as boosting inflammation.

The mice were "perfectly fine . . . except that instead of getting diabetes 90 per cent (of the time), they got none or very little," said Dosch. "Not only did they not get diabetes, but their pancreas was clean - there was no inflammation, no nasties that make the disease in the pancreas."

"That was the real wow."

In other words, a dysfunctional immune response is not the only thing needed to get diabetes - the nerve cells are also critical, he said.

In another experiment, the researchers injected substance P into mice whose islet cells were already inflamed and on the way to being destroyed. By the next day, the inflammation in the animals' pancreatic islets had disappeared.

"That was our first shock. To make an islet clean that's fully inflamed, that's hard," said Dosch.

"The blood glucose normalizes overnight and it stays low for weeks to months - this is with a single shot," he enthused. "We now have four-month-old mice that are non-diabetic that used to be diabetic" - a period equivalent to six to eight years in humans.

While the team isn't about to start injecting humans with substance P, they are planning a study of people with a family history of type 1 diabetes to test for abnormalities in pain sensitivity, which could

point to a higher risk for developing the disease.

Diabetics often suffer from peripheral neuropathy, a condition in the extremities experienced as numbness or as pain described as burning or "pins and needles." The research suggests that neuropathy is not merely a result of diabetes but could be related to the nervous system's role in the whole disease process, Dosch hypothesized.

The sensitivity study is just the first step, he said. "The ultimate goal is to see if substance P would work. If we find that indeed humans and (diabetes-prone) mice are comparable in this respect, then we will be very quick into clinical trials because it's not a toxic trial, it's easy to do."

"In families with the disease where we have good tools, we can identify kids that are at risk and are in progression to disease development. We could step in early and prevent the whole thing from going to completion into overt diabetes. And that would be a great thing."

Commenting on the paper, which appears in Friday's edition of the scientific journal *Cell*, immunologist Terry Delovitch said the work illustrates the importance of not viewing one system of the body in isolation.

"It's an excellent example of system biology, where different systems interact and cross-regulate each other's activity," said Delovitch, a specialist in the immune system and diabetes at the Robarts Research Institute.

"If you're a patient with diabetes, one of the last places to think of a possible cure to come from would be the nervous system," he said Thursday from London, Ont. "It provides now the hope to the population that a component of one system can bring a very positive, potentially preventive effect to a disease in the other system."

"And so new approaches for therapy are going to be even more abundant and provide more hope for treatment of these diseases."

In a commentary accompanying the study, Helene Bour-Jordan and Jeffrey Bluestone of the University of California, San Francisco, Diabetes Center, questioned the researchers' conclusion that the nervous system can alter inflammation and "indirectly affect" the development of autoimmunity.

"An equally plausible possibility is that an autoimmune component targeting the nervous system directly influences the development of autoreactive responses against pancreatic islets," they write, noting that additional studies are needed to confirm which system is the primary catalyst.

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