Experimental bariatric surgery controls blood sugar with diabetic rats

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For the first time, scientists at the Toronto General Hospital Research Institute have shown that an experimental bariatric surgery can lower blood sugar levels in rats with type 1 diabetes.

A team led by Dr. Tony Lam and Dr. Danna Breen, a post- doctoral fellow in the lab of Dr. Lam, used a rat model to study novel nutrient-sensing signals in the jejunum, located in the middle of the intestine. Dr. Lam and his team demonstrate that duodenal-jejunal bypass surgery activates novel nutrient-sensing signals in the jejunum and rapidly lowers blood sugar levels in non-obese rats with uncontrolled diabetes. DJB surgery is a type of bariatric surgery which excludes the duodenum and proximal jejunum, the first section of the small intestine, and instead redirects food into the distal jejunum, the middle to last section of the intestine. This latter section of the intestine, as demonstrated by Dr. Lam and his team, can sense glucose and signal to the brain to let the liver know that it must lower glucose production, leading to better control of blood sugar in the diabetic rats.

The study showed for the first time that a surgical intervention induces a rapid glucose-lowering effect in non-obese type 1 uncontrolled diabetic rats, independent of a reduction in food intake and body weight as well as changes in blood insulin levels.

The research was published in a paper entitled, "Jejunal nutrient sensing is required for duodenal-proximal jejunal bypass surgery to lower glucose levels in uncontrolled diabetes," in the May 20, 2012 on-line

edition of the international journal *Nature Medicine.*

"We report that shortly after a meal, the influx of nutrients into the jejunum of DJB surgical diabetic rats activates novel sensing mechanisms to lower blood sugar levels. Importantly, this occurs in the presence of insulin-deficiency and is independent of weight loss," says Dr. Lam, who holds The John Kitson McIvor (1915 – 1942) Endowed Chair in Diabetes Research and the Canada Research Chair in Obesity at the Toronto General Research Institute and the University of Toronto. He is also Associate Director of Research at the Banting and Best Diabetes Centre at the University of Toronto.

Currently, patients with Type 1 diabetes lower their glucose through insulin injections (usually several times a day) and must regularly monitor blood glucose levels. High or uncontrolled glucose levels can result in damage to eyes, nerves and kidneys and increase the risk of heart attack, stroke, blindness, erectile dysfunction, foot problems and amputations. Many laboratories around the world are in a race to find alternative and effective ways in which to lower and better control glucose levels because of the severe complications which can result from high sugar levels.

Dr. Lam's laboratory is a world pioneer in exploring the role of the gut in regulating blood sugar. "The gut is an easier and therefore more promising therapeutic target in regulating blood sugar than the brain or liver, due to their potential side effects, " says Dr. Danna Breen, who is the lead author in the study. Dr. Breen adds that this type of surgery may potentially have therapeutic value in lowering glucose (sugar) levels in non-obese individuals with type 2 or 1 diabetes, but that many more years of future studies are required to determine whether this approach is effective and safe in humans who have diabetes.

In healthy individuals, insulin is a hormone whose primary role is to

regulate blood sugar. It is produced by cells located on the pancreas in response to sugar intake, and it acts to bring blood sugar to appropriate levels, allowing the body to have the energy it needs to function properly. In persons with type 1 diabetes, the pancreas does not produce insulin, resulting in elevated blood sugar levels due to lack of insulin which cannot signal to the liver to reduce sugar production. People with type 1 diabetes need to take daily insulin shots and carefully monitor their blood sugar levels.

"If new medicines or surgical interventions can be developed that stimulate this sensing mechanism in the gut, we may have an effective and alternative way of slowing down the body's production of sugar, thereby lowering blood sugar levels in diabetes," says Dr. Lam, who is also an Associate Professor of Medicine and Physiology at the University of Toronto. Other ongoing studies of Dr. Lam's lab reveal novel molecular targets in the gut that effectively lower blood sugar in obesity and type 2 diabetes.

Studies reported in the New England Journal of Medicine this year have challenged medical therapy as the prevailing method of treating patients with type 2 diabetes. Two studies reported that bariatric surgery induced remission in severely obese patients with type 2 diabetes, and was associated with significant improvement in metabolic control over and above medical therapy, both conventional and intensive. An accompanying April 26, 2012 editorial by Drs. Zimmet and Alberti, states that "surgeons may now be able to claim greater success in achieving metabolic control", in these patients, although long-term studies with greater numbers of patients still need to be completed. No studies have yet reported on surgical interventions as treatments for patients with type 1 diabetes.

"More than two million Canadians have diabetes. Diabetes is an epidemic in Canada and around the world that is growing at an alarming

rate," says Dr. Philip M. Sherman, Scientific Director of the Institute of Nutrition, Metabolism and Diabetes at the Canadian Institutes of Health Research. "Since many people are undergoing bariatric surgery in an attempt to manage morbid obesity and the associated health problems, such as diabetes, it is critical that we understand how it works. The Canadian Institutes of Health Research is pleased to support Dr. Lam's work which increases our understanding and may offer a new approach to managing morbidity and premature mortality resulting from this illness."

Working with rats, Drs. Lam, Breen and colleagues designed and performed a series of elegant experiments on two different groups of rats: rats whose insulin-producing pancreatic islet cells were destroyed by toxins; and genetically-altered rats which experienced spontaneous autoimmune destruction of islet cells – similar to what happens in humans with type 1 diabetes.

Non-obese rats induced with uncontrolled diabetes or autoimmune type 1 diabetes had an experimental DJB surgery, a variation of the Roux-en-Y gastric bypass, the most common surgical method currently used to treat obese patients. Two days after DJB surgery, blood sugars were normal in the insulin-deficient diabetic rats.

Dr. Breen emphasized that further studies need to be undertaken to determine the long-term effects of this intervention in rodents, as well as to ensure the safety and efficacy of this procedure in humans.

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