

Potential drug target identified for diabetes by studying novel gut-brain-liver circuit

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Scientists at the Toronto General Hospital Research Institute have discovered a novel signaling pathway between three organs – the gut, the brain, and the liver – which lowers blood sugar when activated.

A team led by Dr. Tony Lam used a rat model to discover that fats can activate a subset of nerves in the intestine, which then send a signal to the brain and subsequently to the liver to lower glucose or sugar production. But eating a high-fat diet for just three days can interfere with this signal, disabling it so that it does not signal the other organs to lower blood glucose levels.

The research was published in a paper entitled, “Upper intestinal lipids trigger a gut-brain-liver axis to regulate glucose production” as an advance on-line publication of the international science journal *Nature*.

“This is a new approach in developing more effective methods to lower glucose or blood sugar levels in those who are obese or have diabetes,” said Dr. Lam, who holds The John Kitson McIvor (1915 – 1942) Chair in Diabetes Research at the University Health Network and University of Toronto. Currently, those with diabetes lower their glucose through diet, exercise, anti-diabetic tablets or insulin injections (usually several times a day) and must regularly monitor blood glucose levels. High 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 glucose

levels because of the severe complications which can result from high sugar levels.

“We already knew that the brain and liver can regulate blood glucose levels, but the question has been, how do you therapeutically target either of these two organs without incurring side effects?” noted Dr. Lam, who is also an Assistant Professor of Physiology and Medicine at the University of Toronto. “We may have found a way around this problem by suggesting that the gut can be the initial target instead. Much like a remote control device, the gut is able to relay a signal to the brain which in turn signals the liver to lower glucose production. If new medicines can be developed that stimulate this sensing mechanism in the gut, we may have an effective way of slowing down the body’s production of sugar, thereby lowering blood sugar levels in diabetes.”

Dr. Lam emphasized that it will take a number of years of experimental work to determine whether this approach is effective and safe in humans who have diabetes.

More than two million Canadians have diabetes. “Diabetes is an epidemic in Canada and around the world and its numbers are continuing to increase at an alarming rate, consuming our precious health care resources,” says Dr. Gary Lewis, Head of the Division of Endocrinology and Metabolism at the University Health Network and Mount Sinai Hospitals in Toronto and Professor of Medicine and Physiology at the University of Toronto. “We have good evidence from clinical trials which shows that lowering blood glucose levels towards normal in those who develop diabetes has a major impact in preventing its devastating complications, so it is critical that we learn how to control these levels in the most effective and least invasive ways possible. Dr. Lam’s work reveals a new regulatory circuit which provides novel sites and targets to lower these levels in diabetes and obesity.”

Dr. Richard Weisel, Director of the Toronto General Research Institute (TGRI), Professor and Chairman of Cardiac Surgery at the University of Toronto, welcomes any potential interventions which can help lower blood sugar levels. “Studies have shown that people with very high blood glucose levels are more likely to die from heart disease, so anything that we can discover to help lower these levels would help in decreasing the progression of and mortality from cardiovascular disease.”

"Tony's discovery represents an exciting breakthrough that could eventually lead to new ways to treat diabetes," observed Dr. Diane Finegood, Scientific Director of the Institute of Nutrition, Metabolism and Diabetes, part of the Canadian Institutes of Health Research (CIHR). "I am pleased that CIHR played a major role in funding this research".

Working with rats, Dr. Lam and colleagues designed and performed a series of elegant experiments which showed for the first time that the lipids or fats which enter the small intestine trigger the afferent neuronal signal to the brain which then sends signals to the liver to lower glucose production and blood glucose levels in as little as fifteen minutes. No drop in levels occurred when nerves were cut or blocked between the gut and the brain or between the brain and the liver. The trigger to lower glucose was also disabled when rats were fed a high-fat diet for three days prior to the experiment, a finding which may suggest that those who eat a high fat diet lose this beneficial signaling pathway.

Source: Canadian Institutes of Health Research

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