



Solving a critical part of the insulin puzzle

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We are now one step closer to improved treatment of Type 2 diabetes following significant findings made by scientists at the Garvan Institute of Medical Research. World-wide, more than 200 million people suffer from this disease, resulting in disability and reduced life expectancy. In Australia it affects around 7% of our population.

People with Type 2 diabetes do not produce enough insulin, a hormone made in the pancreas that helps convert the sugar in our blood into energy in our muscles. Current therapies force our bodies to make more insulin, make better use of the insulin that already exists or mimic the action of insulin. But none of these therapies specifically address the reasons why insulin production fails in the first place.

The team from Garvan's Diabetes Signalling Unit, led by Associate Professor Trevor Biden and Dr Carsten Schmitz-Peiffer, has identified an enzyme known as "PKCepsilon" (PKCe) that is active during diabetes and blocks the availability of insulin. Their findings are published today in the prestigious international journal, *Cell Metabolism*.

"In PKC, we believe we've identified a very important biological target that will enable us to address one of the major underlying causes of diabetes," said Biden. "The next step is to develop a targeted pharmaceutical that will inhibit PKCe and allow the insulin producing cells of the pancreas to do their job."

"While current therapies can force the body to produce more insulin, no existing drug does what a PKCe inhibitor would do, and that is to act only on the diabetic pancreas, allowing it to produce insulin when most needed, just as glucose levels rise after a meal. In other words, we'd be restoring normal function."

Biden and Schmitz-Peiffer have been studying the relationship between fat oversupply and Type 2 diabetes for many years. Far from being an inert substance, fat contains molecules that bring about complex changes in the way our bodies produce and use insulin. Specifically, fat molecules reduce the ability of muscle cells to respond to insulin, a phenomenon known as 'insulin resistance'. Most of us cope with this by producing more insulin, but people who develop diabetes can't, probably because fat molecules also disrupt the glucose-sensitive, insulin-producing ('beta') cells in their pancreas.

"Our recent research shows that absence of PKCe restores the capacity of the pancreas to produce insulin, a result we were not expecting," said Schmitz-Peiffer. "Genetically modified mice, without PKCe, were fed high fat diets and became fat and insulin resistant but failed to develop diabetes. Instead, they produced extra insulin."

“What this tells us is that we will be able to protect people at high risk of developing diabetes from losing the ability to produce insulin. Blocking PKCe won't stop them from becoming insulin resistant, but it will restore their capacity to compensate. Fine-tuning insulin production in this way is a big advance on current drugs targeting the pancreas, which can overstimulate beta cells and so reduce the effectiveness of insulin.

“In the world of diabetes research, this is a ground-breaking discovery. It's like slotting in a critical part of a jigsaw puzzle, a part that suddenly makes the whole picture much clearer.”

The work of Trevor Biden and Carsten Schmitz-Peiffer forms part of a large Diabetes and Obesity research program at Garvan, in which clinicians and scientists work together to investigate the complexities of a disease that is affecting increasingly larger proportions of the world's population.

NOTES TO EDITORS

The paper, to be published online in Cell Metabolism, will be a featured article. This means that the editors believe the content is newsworthy for a scientific audience, and will include an editorial commentary.

The title of the paper is: *Inhibition of PKCe Improves Glucose-Stimulated Insulin Secretion and Reduces Insulin Clearance*

In addition to the benefits mentioned in the release, PKCe also reduces the rate of insulin clearance from the liver, making more available in the system.

ABOUT GARVAN

The Garvan Institute of Medical Research was founded in 1963. Initially a research department of St Vincent's Hospital in Sydney, it is now one of Australia's largest medical research institutions with approximately 400 scientists, students and support staff. Garvan's main research programs are: Cancer, Diabetes & Obesity, Arthritis & Immunology, Osteoporosis, and Neuroscience. The Garvan's mission is to make significant contributions to medical science that will change the directions of science and medicine and have major impacts on human health. The outcome of Garvan's discoveries is the development of better methods of diagnosis, treatment, and ultimately, prevention of disease.

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