



## **Regulating the sugar factory in diabetes**

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Scientists in Sydney and Boston believe they may have identified a gene that controls abnormal production of sugar in the liver, a very troublesome problem for people with diabetes.

The liver is the sugar factory for the body - when blood sugar (glucose) levels fall, the liver makes and releases more. In people with diabetes, especially Type 2 diabetes, the liver doesn't stop making sugar when it should, so blood sugar levels can rise overnight while they sleep even though they haven't eaten.

Dr Jenny Gunton, diabetes specialist and endocrinologist from Sydney's Garvan Institute of Medical Research, in collaboration with Dr Xiao Hui Wang and Professor Ronald Kahn from Harvard Medical School and Joslin Diabetes Centre in Boston, have published their findings in the journal *Cell Metabolism*, now online.

"A lot of my patients will complain that they go to bed with a blood sugar of 5 and wake up with a blood sugar of 12," said Dr Gunton.

"It upsets people when their blood sugar behaves as if they're getting up in the night and having a really big snack. I have to tell them it's just one of those unfair things about having diabetes."

People with Type 2 diabetes do not produce enough insulin in the pancreas after a meal. At the same time, they are less able to use that insulin to move glucose into fat and muscle cells, a condition known as 'insulin resistance'.

With her colleagues in Boston, Gunton has been studying a transcription factor, or kind of 'master regulator', called ARNT, which controls expression of other genes involved in processes like glucose breakdown and insulin production. In an earlier study, the group showed that there is 90% less ARNT in insulin-producing cells of people with Type 2 diabetes.

The current study looks at how ARNT might be affecting the liver, and its results confirmed Dr Gunton's suspicions. "We've shown that there's likely to be decreased ARNT in the liver of people with Type 2 diabetes compared to people without Type 2 diabetes," she said.

"Working with mice, we found that glucose levels were elevated and there was glucose production from a 'precursor', a source not normally metabolised."

Other results in the study show that to some extent ARNT is regulated by insulin, so that insulin resistance in itself will contribute to a decrease in ARNT. If liver cells are treated with insulin, there will be a small increase

in ARNT protein. The insulin will also help move the ARNT into the nucleus of the cell, where it does its job as a master regulator.

The paper concludes that a decline in ARNT isn't limited to the beta cells of people with Type 2 diabetes. ARNT is also reduced in other important diabetes-related tissues like the liver.

Dr Gunton believes that if a new drug could be developed to increase ARNT activity in the liver, then it may be possible to shut down abnormal sugar production and improve blood sugar control in people with diabetes.

## **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 nearly 500 scientists, students and support staff. Garvan's main research programs are: Cancer, Diabetes & Obesity, Immunology and Inflammation, Osteoporosis and Bone Biology, 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.

### **All media enquiries should be directed to:**

Alison Heather

Science Communications Manager

+61 2 9980 1224

+61 434 071 326

[a.heather@garvan.org.au](mailto:a.heather@garvan.org.au)