

The free radical that triggers insulin resistance and Type 2 diabetes

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Australian scientists have identified a 'free radical' that appears to trigger insulin resistance, or glucose intolerance, one of the first stages in the development of Type 2 diabetes.

It has been known for decades that being overweight or eating too much sugar and fat can lead to insulin resistance, but until now no-one has identified the central mechanism, or cellular switch, that initiates the process.

A group of scientists from Sydney's Garvan Institute of Medical Research, led by Dr Kyle Hoehn and Professor David James, believe they may have found that elusive switch.

Hoehn and colleagues have found that overeating may stimulate the conversion of the oxygen in the air we breathe into toxic free radicals, leading to insulin resistance. They have also found that neutralising this 'conversion pathway' may reverse insulin resistance in animals. These important findings are published online this week in the prestigious international journal Proceedings of the National Academy of Sciences (PNAS).

"When we breathe in oxygen it's used, in combination with the food that we eat, to produce energy," said Professor David James, Director of Garvan's Diabetes and Obesity Research Program. "Occasionally it's also converted to free radicals – but normally that's kept to a minimum."

"Our study shows that this radical conversion pathway appears to move up a gear when there's too much food, or a surplus of energy, in the system."

"The key to this observation is that the free radicals that cause insulin resistance appear to be superoxides, made mainly in a specific cellular compartment called the mitochondria. This is important, as it means that many antioxidants available 'off-the-shelf' may not work as they probably do not reach the mitochondria."

"Pregnancy, lack of exercise and a range of medical conditions can also bring about insulin resistance. In this study, we show that mitochondrial superoxide is the common feature in all instances of insulin resistance, no matter how it's induced."

Co-author on the project, Dr Nigel Turner, explained the finding from a slightly different perspective. "Insulin resistance appears to be a natural defence mechanism. It's our cells' way of saying 'don't give me any more food'," he explained.

"The superoxides we've identified seem to trigger an intracellular process that shuts down acceptance of fresh nutrients, because the body doesn't want any more."

"Glucose transport molecules stop travelling to the cell surface to allow fresh supplies to enter. That in turn leads to high blood sugar levels and associated complications."

"We showed in mice that you can reverse the process by blocking superoxides, either genetically or with pharmacological agents."

"Once you remove superoxides, or the ability of mitochondria to produce them, insulin action resumes, glucose transporters become more active and blood sugar levels return to normal."

The findings are encouraging because identifying the mechanistic origin of insulin resistance is a very important first step for identifying diabetes therapies in the future. Mitochondrial superoxides would have to be very specifically targeted with drugs developed for that purpose.

The Diabetes Research Foundation (DRF) commends the Garvan Institute for these research findings.

We need your ongoing support so that vital and important research continues into all aspects of diabetes. You can support us via the DRF website or contact:

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