



Beating Diabetes

BY MIA AKERFELDT

A chemical compound that acts as a “saviour” of dying insulin cells could provide a therapy for Type 2 diabetes.

It is now widely acknowledged that high levels of fat and obesity are major contributing factors in many diseases, including Type 2 diabetes.

Research has shown that fat causes stress in insulin cells. This stress is capable of killing the insulin cell and leading to the development of diabetes. Now a recent study has shown that a small chemical compound that relieves this stress can prevent fat from killing insulin cells.

Type 2 diabetes is a growing epidemic

associated with obesity and the Western lifestyle. As the proportion of people who are obese is rising, the number of newly diagnosed cases of Type 2 diabetes is escalating, and only this year about 100,000 Australian adults developed the disease. Due to treatment requirements for the many complications of diabetes and the fact that there is no cure available, the cost of diabetes in Australia is more than \$3 billion per year.

Diabetes is a disease characterised by

excessive levels of sugar in the blood. After a meal, carbohydrates in our food are broken down into sugar (glucose) and eventually absorbed into tissues throughout the body, such as the brain, muscles and fat.

Type 2 diabetes develops when the body cannot absorb the sugar in our food, resulting in excessive levels in the bloodstream. These high sugar levels may have a severe impact on various parts of the body. For example, it may lead to blind-

ness, kidney damage, reduced wound healing and increased risk of stroke and heart attack.

BLOOD GLUCOSE REGULATION

Glucose circulates through the bloodstream and is taken up by tissues throughout the body to be used as energy. Despite fluctuations in the supply of energy from the diet during the day, the glucose level in the blood remains relatively stable. This is because insulin secreted by the beta-cells in the pancreas stimulates the uptake of glucose into the body's tissues.

Binding of insulin to a receptor on the outside of muscle or fat cells signals to the cells' glucose transporters to absorb the glucose from the bloodstream. Sometimes, often in association with obesity, the signal from the insulin receptor to the glucose transporters becomes blunted, and less glucose is taken up into the cell. This phenomenon is known as insulin resistance, and is a common feature of Type 2 diabetes.

At first the body responds by secreting more insulin, and this helps to overcome the insulin resistance. However, eventually the beta-cells fail to compensate for this defect in insulin signalling and Type 2 diabetes arises.

The failure of the beta-cells is due to both a reduction in their numbers and their ability to secrete insulin. As a result, a combination of insulin resistance and beta-cell failure leads to the development of Type 2 diabetes.

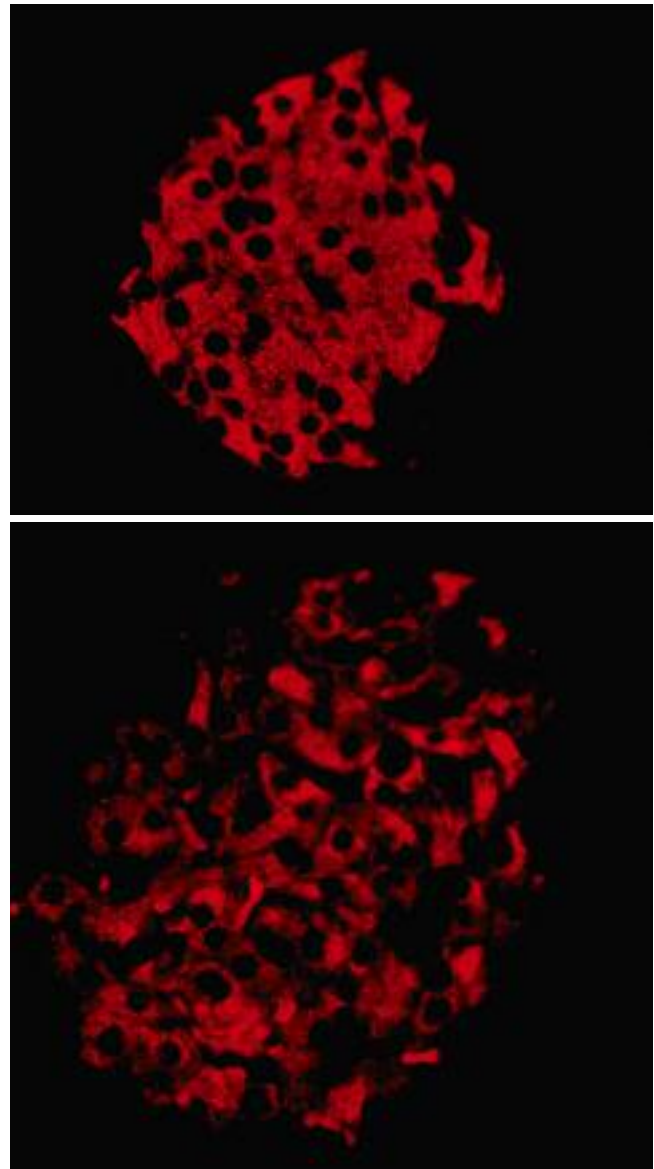
There is currently no cure for Type 2 diabetes, but it can be treated with changes in diet and exercise that can partially reverse the insulin resistance and improve the function of the pancreatic beta-cells. However, often diet and exercise changes are not sufficient to reverse the diabetes and drug treatment is required.

Current drugs for Type 2 diabetes work by either improving the tissues' ability to take up glucose or enhancing the output of insulin from the pancreas. Unfortunately, these drugs do not stop the disease progression and often insulin injections are required.

THE INSULIN FACTORY

The beta-cells are specialised cells in the pancreas. Their main function is to regulate blood glucose levels by making and releasing insulin. They are found in little balls of cells called the islets of Langerhans, which make up only 1–2% of the pancreas. The rest of the pancreas is responsible for secreting pancreatic juice containing digestive enzymes into the intestine. This function of the pancreas is generally not affected in diabetes.

The beta-cell makes vast amounts of insulin, and therefore can be thought of as a protein factory. The beta-cell is carefully divided into compartments, each with its own specialised function in the making of a protein. Proteins such as insulin are



Insulin staining in non-diabetic (top) and diabetic (bottom) islet cells. The diabetic islets are disorganised and contain less insulin compared with non-diabetic islets.

made from the DNA blueprint that contains the information on how to make the protein and each protein has its own specific gene encoding for it.

The first step in protein synthesis occurs in the nucleus compartment of the cell and involves the making of messenger RNA from the DNA blueprint. The messenger RNA travels from the nucleus into the cytoplasm of the cell where it eventually meets the ribosome. The ribosome will read the code from the RNA and make a polypeptide (i.e. a string of amino acids).

To become a functional protein, this string of amino acids now needs to be modified, folded or curled into its final structure. This folding and modification of proteins occurs in the endoplasmic reticulum (ER) and is facilitated by chaperone proteins. These are thought to assist new proteins to fold by



Mia Akerfeldt has found that the mechanisms leading to Type 1 and Type 2 diabetes are different, but that a chemical compound can prevent or slow down the development of Type 2 diabetes.

inhibiting alternative assembly pathways that produce non-functional structures.

A protein such as insulin cannot be released from the ER until it has been correctly folded. Sometimes, when too many proteins enter the ER at the same time, there are not enough chaperones to cope with the increased load. Consequently, proteins may become trapped in the ER and prevented from reaching their final destinations in the body.

This gridlock of proteins induces a state termed “ER stress”. This not only affects the release of insulin but if the stress is prolonged it can cause the cells to die.

FAT CAUSES STRESS

In a landmark study our research group has showed that ER stress is present in the beta-cells of patients with Type 2 diabetes. We also showed that exposure of mouse beta-cells to saturated fat caused ER stress and accelerated beta-cell death, similar to what occurs in Type 2 diabetes patients. We therefore hypothesised that fat might cause ER stress and that this may contribute to the loss of beta-cells and the development of Type 2 diabetes.

Recently another research group

reported that a phenyl butyric acid (PBA) could reduce ER stress in an animal model of obesity and Type 2 diabetes. PBA is a chemical chaperone that is thought to improve the ER folding capacity by helping proteins fold and improving the efficiency of the cell’s own chaperones.

We tested our hypothesis by treating beta-cells with fat together with the chemical chaperone PBA. In these experiments PBA reversed ER stress caused by fat. Importantly, we also showed that this treatment completely prevented the cell from dying, indicating that this compound could potentially prevent or slow down the development of Type 2 diabetes. At least in laboratory experiments and in animals, the compound shows potential as a therapeutic agent for preventing beta-cell death in Type 2 diabetes.

The compound PBA has already been approved by the Food and Drug Administration in the United States for use in another clinical application, which means that the drug has been extensively tested in humans to prove that it has an outstanding safety profile. We are therefore greatly anticipating the results from a research group in Canada that is

currently testing the effects of this compound on insulin secretion in humans.

Although, the use of chemical chaperones like PBA may prove to be useful in the treatment of obesity-induced Type 2 diabetes, it is important to note that lean individuals also develop Type 2 diabetes, suggesting other environmental or genetic contributions to the development of the disease.

ER STRESS IN TYPE 1 DIABETES?

In Type 1 diabetes the islet of Langerhans are invaded by the body’s own immune system, causing inflammation in the beta-cells. This inflammation is promoted by cytokines secreted by immune cells, and prolonged exposure to these cytokines leads to beta-cell death.

Until now, it was thought that the processes leading to beta-cell death were similar in both Type 1 and Type 2 diabetes. We tested whether cytokines, similar to fat could cause ER stress and cell death. Indeed, cytokines induced ER stress in the cells, and this stress could be prevented using the chemical compound PBA. Surprisingly, in contrast to our fat studies, reducing ER stress did not prevent the beta-cells from dying. Therefore PBA may not have the potential to prevent beta-cell death in Type 1 diabetes, although further testing is required.

CONCLUSION

To summarise, our studies have for the first time shown that the mechanisms of beta-cell loss in Type 1 and Type 2 diabetes are quite different. We identified that there is a potential for treating Type 2 diabetes by reducing the level of stress in the beta-cell using the chemical compound PBA.

So is this “the cure” for diabetes? We don’t know yet but we await with excitement the results from the clinical trials.

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