Scientists identify key control for blood glucose levels which could improve diabetes treatment

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For people suffering from diabetes, managing blood sugar can be like walking a tightrope - if too high they run the risk of serious long term complications such as blindness, kidney failure, limb gangrene and premature heart disease, but allow it to drop too low and it can lead to a loss of consciousness which could be fatal.

Now a team of scientists from the UK and USA, has taken a major step forward in understanding how the brain senses low glucose levels and triggers responses to deal with this, which could help clinicians to devise new strategies to help control diabetes more safely.

They have identified a completely novel and hitherto unsuspected pathway buried deep within a region of the brain called the parabrachial nucleus. Here they found that a brain hormone, cholecystokinin (CCK), is a crucial sensor of blood glucose levels and orchestrates responses around the body when levels drop too low.

Professor Lora Heisler, from the University of Aberdeen Rowett Institute of Nutrition and Health, said: "It is remarkable to find that such an incredibly small set of cells in the brain play such an important role in maintaining normal glucose levels."

Dr Martin Myers, from the University of Michigan, said "We knew that CCK cells in the brain modify things like appetite and anxiety but they had previously been overlooked in terms of any link to blood sugar levels.

"The discovery of the important function of this brain hormone raises the possibility of using drugs targeting the CCK system to boost defences against hypoglycaemia, the clinical syndrome that results from low blood sugar. This can be extremely serious and in the most severe cases can lead to seizures, unconsciousness, brain damage and even death."

Professor Heisler and Dr Myers collaborated with colleagues from the universities of Aberdeen, Michigan, Cambridge, Edinburgh and Chicago to complete the study and their findings are now published in the journal *Nature Neuroscience*.

Professor Heisler said the identification of the role played by CCK could be of particular significance to around 20% of patients with diabetes who suffer from regular severe debilitating episodes brought on by low blood sugar.

"To allow glucose to enter the cells and provide the body with the energy it needs to carry out all basic functions, insulin is needed," Professor Heisler added.

"For those with diabetes, the effects of insulin on the body are drastically diminished, either because the pancreas doesn't produce enough of it (type 1 diabetes) and/or because cells are less responsive to it (type 2 diabetes).

"As a result, glucose can build up in the bloodstream and may reach dangerously high levels (hyperglycemia) which can result in serious long term complications such as blindness, kidney failure, limb gangrene and amputation and premature heart disease.

"To correct this problem, diabetics take insulin or other drugs designed to lower blood sugar levels but if they take too much insulin relative to the amount of glucose in their bloodstream, it can cause your blood sugar level to drop too low, resulting in hypoglycaemia.

"When patients suffer repeated bouts of hypoglycaemia they can develop 'unawareness' which means they find it difficult to detect symptoms that their blood sugar levels are falling and it is this group particularly that we hope could benefit from our findings in regard to the role played by CCK."

Dr Myers was the lead researcher in the study and now hopes to apply their findings in a clinical environment.

He said: "When blood sugar levels drop, a cascade of events takes place within the body which should boost it back up to normal levels but we did not know what triggered this chain of events.

"By identifying and understanding the basic machinery – CCK – that is organising and orchestrating this cascade of events, the more we can use that mechanism to help treat this disease.

"Further research is now needed to look at how we can target the CCK system as well as the cells upon which CCK acts to prevent or treat hypoglycaemia."

More information: "Leptin-inhibited PBN neurons enhance responses to hypoglycemia in negative energy balance." *Nature Neuroscience* 17, 1744–1750 (2014) DOI: 10.1038/nn.3861

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