Putting type 2 diabetes into remission: Moving towards non-surgical interventions in the future

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Diabetes currently affects approximately 415 million people worldwide, with over 4 million people living with the condition in the UK alone (International Diabetes Federation, 2015). Diabetes and its complications cost the NHS £9 billion every year, which is equivalent to 10% of the total health budget (Hex et al, 2012).

Importantly, people with diabetes face many daily challenges, including insulin injections, unpleasant side effects and a struggle to achieve optimal diabetes control. These factors significantly impact on their day-to-day living and quality of life. Unfortunately, medications can only manage the symptoms of diabetes.

Exploring the biology of gastric bypass surgery

Although developed originally as a weight reduction therapy, gastric bypass surgery can also lead to rapid remission of type 2 diabetes, as well as other associated illnesses and complications, without the subsequent need for any medication (Buchwald et al, 2004). The reversal of high blood glucose levels is independent of weight loss, but the mechanisms behind this phenomenon remain largely unknown.

Type 2 diabetes is increasingly being recognised as a bihormonal condition, characterised not only by insufficient insulin secretion but also by an impairment in glucagon regulation (Unger and Cherrington, 2012). Pancreatic islets are centre stage in diabetes and play a fundamental role in glucose homeostasis, but the impact of Roux-en-Y gastric bypass (RYGB) on islet function, especially in terms of glucagon secretion, has not yet been explored thoroughly.

To date, the role of the incretin hormone glucagon-like peptide-1 (GLP-1) in the metabolic improvements that occur post-surgery remains inconclusive. It is also not yet known whether RYGB can correct both insulin and glucagon secretory defects in people with type 2 diabetes.

Using a lean rat model of type 2 diabetes and techniques not possible in humans, we recently reported our investigations on the impact of RYGB on pancreatic islet function and structure (Ramracheya et al, 2016).

The hormone PYY plays a significant role in islet function restoration

We set out to understand the underlying mechanisms behind the beneficial effects of RYGB and found that the surgery normalised glycaemia in the type 2 diabetes rat model by restoring the function of the pancreatic islets. In islets isolated from the rats, the surgery resulted in improved glucose-stimulated insulin secretion and glucagon suppression. RYGB also influenced islet gene transcription – with increased gene expression levels for insulin and glucagon – and restored islet morphology.

It was initially believed that GLP-1 could be responsible for the improved glucose homeostasis and remission of type 2 diabetes following the surgery. However, previous research has hinted that an alternative mechanism may exist, showing that the beneficial effects of RYGB persist in mice lacking in both GLP-1 and its receptor (Mokadem et al, 2013; Ye et al, 2014).

As such, we found that the restoration of islet function, and the subsequent restoration of insulin and glucagon secretion, was mediated by another hormone secreted by the L-cells of the intestinal tract in response to glucose intake: peptide tyrosine tyrosine (PYY). Levels of PYY are drastically reduced in obesity and type 2 diabetes (Batterham et al, 2003), and animal studies have shown that exogenous PYY inhibits food intake and weight gain, whilst mice lacking the hormone eat excessively and develop obesity (Pittner et al, 2004).

Our finding that PYY improved the function of isolated human islets suggests that our observations could be extended from rats to humans. Significant increases in serum PYY levels following bariatric surgery have been reported (Chan et al, 2006). However, the role of PYY on pancreatic islet function, particularly in humans, is largely unexplored.

Moving forward

Further studies are now needed to address whether the beneficial effects of RYGB are sustained over the long term, and to investigate whether a pharmacological agent stimulating PYY production or mimicking its action could provide an effective and non-surgical therapy for type 2 diabetes.

These findings are extremely timely, given the growing urgency to develop non-surgical alternatives to weight loss surgery that can be used to stem the rising tide of obesity and type 2 diabetes. We hope to test whether PYY mediates the anti-diabetes effects of RYGB, through the regulation of insulin and glucagon secretion in islets. These studies will generate information immediately relevant to the development of new non-surgical or pharmacological therapies that can target type 2 diabetes and obesity in the future. ■

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