SURGERY

Balancing glucose levels after bariatric surgery — an important role for GLP1

GLP1 is a very important driver of insulin secretion after gastrectomy surgery

After bariatric surgery, many patients experience resolution of type 2 diabetes mellitus before they have lost a notable amount of weight. However, the mechanisms underlying this effect have been unclear. Now, new research suggests that glucagon-like peptide 1 (GLP1) has a key role in initiating insulin secretion following bariatric surgery, which could account for the rapid resolution of type 2 diabetes mellitus.

“We wanted to understand the contribution of the gut endocrine system to the control of blood glucose,” says corresponding author Fiona Gribble. Studying the role of the gut endocrine system in patients with obesity who have undergone bariatric surgery is challenging, as these patients are also losing weight after the surgery. “Instead, we studied a cohort of normal-weight patients who had familial gastric cancer,” explains Gribble. These patients had undergone gastrectomy, in a similar procedure to bariatric surgery. The patients with gastric cancer were lean, and after gastrectomy they exhibited similar hormonal changes to those seen in patients with obesity after bariatric surgery, namely, increased levels of GLP1, peptide YY and insulin. Following gastrectomy,

these patients were also prone to hypoglycaemia.

To examine the role of GLP1, the researchers gave patients either exendin 9 (to block the GLP1 receptors) or a placebo. “We found that when the participants had an exendin 9 infusion at the same time as a glucose drink, they did not produce as much insulin and did not develop hypoglycaemia,” explains Gribble. “The exendin 9 experiment showed that GLP1 is a very important driver of insulin secretion after gastrectomy surgery.” Indeed, lean patients who had undergone gastrectomy had peak insulin levels that were approximately twofold higher than those seen in control patients, and administration of exendin 9 restored these levels to normal.

To further examine the role of GLP1, the researchers carried out either vertical sleeve gastrectomy (VSG) or a sham control operation on lean mice. The mice were then given a GLP1 receptor blocker or a control antibody for 12 weeks. During this 12-week period, the mice received 4 weeks of a liquid diet, 4 weeks of a high-fat diet and 12 days of a control low-fat diet. While on the high-fat diet, the mice that underwent VSG and received the GLP1 receptor blocker ate more than the VSG mice on the control antibody, and showed a tendency to gain more weight. This finding suggests that endogenous GLP1 suppresses food intake on a high-fat diet. In addition, plasma concentrations of glucose were increased in all mice that received the GLP1 receptor blocker and insulin levels were reduced in the VSG mice that received the blocker compared with those that received the control. Transcriptome and peptidome analysis of biopsy samples from the

mice and the lean patients who had undergone gastrectomy revealed that bariatric surgery does not change the functional output of enteroendocrine cells. “In the tissue samples and mouse models, we showed that the increased GLP1 does not arise because the gut changes which hormones it produces or where they are produced,” explains Gribble. “Instead our data suggest that nutrients are absorbed lower down the gut after surgery, and that this stimulates more of the GLP1-secreting cells, which are found in higher numbers in the lower gut.” Using fluorescein isothiocyanate dextran, the researchers were able to demonstrate that intestinal transit was increased in mice that had undergone VSG, which suggests that nutrients pass through the upper gut more quickly after bariatric surgery and are absorbed in more distal regions of the gut.

In the future, Gribble and colleagues hope to examine whether blocking GLP1 in the long term would be effective in humans. This approach could improve the poor appetite and adverse effects after eating that are currently experienced by patients who undergo gastrectomy during cancer treatment and by patients who undergo bariatric surgery. “The long-term aim would be to develop pharmacological ways to stimulate gut endocrine cells, and thereby to produce the effects of bariatric surgery in patients with obesity who have type 2 diabetes mellitus, but without the bariatric surgery,” concludes Gribble.

Claire Greenhill

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