Isolated Duodenal Exclusion Improves Glucose Homeostasis by Both Weight Loss-Dependent and Independent Mechanisms in Diet-induced Obese Rats

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BACKGROUND

• After Roux-en-Y gastric bypass (RYGB), glycemic control in type 2 diabetic (T2D) patients usually occurs before any significant weight loss.
• This early glycemic control suggests the activation of weight-loss independent mechanisms of glucose control activated after the surgical manipulation of the gastrointestinal tract.
• RYGB is a complex procedure that includes five anatomical components (figure 1A). Evidence suggests that nutrient exclusion from duodenum as well as early delivery of partially digested nutrients to the distal jejunum are key components of RYGB involved in glucose control.
• To study the role of these components in isolation, we have developed a rat model of the the endoluminal sleeve (ELS) device (figure 1B).

METHODS

• Twenty age and weight-matched DIO male Sprague-Dawley rats were allocated in 4 groups: sham operated (SO, n=5), 1 cm (ELS-1, n=5), 4 cm (ELS-4, n=5), and 10 cm (ELS-10, n=5). All rats were kept on a liquid diet one week after surgery. After one week, all rats were given ad libitum access to a high fat diet.
• We evaluated body weight progression, fasting glycemia (FG), insulin sensitivity by HOMA-IR, oral glucose tolerance (OGTT), and glucose stimulated insulin secretion (GSIS).

AIM

• To explore the contribution of different degrees of isolated nutrient exclusion from duodenum, and early delivery of partially digested nutrients to distal jejunum on glucose homeostasis

RESULTS

Complete nutrient exclusion from duodenum induces a greater improvement in glucose homeostasis than that induced by weight loss and caloric restriction

• We studied the effect of weight loss, and caloric restriction on glucose homeostasis in a group of rats that were matched to the final weight of the ELS-10 (weight-matched sham, WMISO), and in a group of rats pair-fed to the food intake of ELS-10 rats (pair-fed sham, PFSD). Despite a similar final weight, or energy intake, ELS-10 treated rats had lower FG (figure 4A), and a better OGTT (figure 4B) than WMISO, PFSD, and SO control rats.

SUMMARY OF RESULTS

• Complete, and not partial nutrient exclusion from duodenum is required to induce the greatest improvement in glucose tolerance, and insulin sensitivity
• In contrast, fasting glycemia was improved in a similar proportion regardless the length of the excluded duodenum
• Implantation of a 10 cm ELS enhanced the benefits of weight loss, and caloric restriction on several parameters of glucose homeostasis
• The greater improvement in overall glucose homeostasis observed in ELS-10 rats was associated with and increased incretin response, that was independent of the ELS-10 induced weight loss

CONCLUSIONS

• The dose-response relationship between ELS length and improvement in glucose homeostasis suggests its metabolic regulation by signals arising throughout the proximal small intestine
• Improvement in glucose homeostasis after complete nutrient exclusion from duodenum results from weight loss dependent and independent mechanisms
• Implantation of a 10 cm ELS induced a unique weight loss independent effect on GLP-1 secretion
• All together these results suggest, that isolated complete nutrient exclusion from duodenum is sufficient to mimics the benefits of RYGB on glucose homeostasis

Figure 1: A) RYGB. The procedure for RYGB is as follows: 1) isolation of the proximal stomach, 2) exclusion of the distal stomach from nutrients contact, 3) exclusion of the duodenum and proximal jejunum from nutrient contact, 4) early contact of partially digested nutrients with jejunum, and 5) partial vagotomy. B) ELS. After implantation of a 10 cm ELS, ingested nutrients flow through the ELS lumen, while bilipancreatic secretions (2) remain external to the device lumen and are diverted distally in the small intestine (3). Thus, a 10 cm ELS mimics in isolation these two components of RYGB

Figure 2: A) ELS-treated rats improved FG to a similar extent. B) Complete nutrient exclusion from duodenum induces the greatest improvement in insulin sensitivity. • p<0.05 vs SO, ** p<0.05 vs all groups.

Figure 3A: Complete nutrient exclusion from duodenum induced a greater improvement in glucose tolerance. • p<0.05 vs SO, ** p<0.05 vs all groups.

Figure 3B: Glucose stimulated insulin secretion was significantly reduced after complete nutrient exclusion from duodenum reflecting improved insulin sensitivity. • p<0.05 vs SO

Figure 4: A) Complete nutrient exclusion from duodenum increased the benefit of weight loss and caloric restriction on fasting glycemia, and B) oral glucose tolerance. • p<0.05 vs SO, ** p<0.05 vs all groups.

Figure 5: A) Glucose stimulated insulin secretion was significantly reduced in WMISO, and ELS-10 rats. B) Complete nutrient exclusion induces a greater improvement on insulin sensitivity than weight loss and caloric restriction. • p<0.05 vs SO, ** p<0.05 vs all SO and PFSD, *** p<0.05 vs all groups

Figure 6: A) Fasting GLP-1 levels are increased in WMISO, and ELS-10 rats. B) ELS-10 significantly increases GLP-1 secretion in response to glucose. • p<0.05 vs SO, ** p<0.05 vs SO and WMISO

Figure 2A: Glucose stimulated insulin secretion was significantly reduced after complete nutrient exclusion from duodenum reflecting improved insulin sensitivity.

Figure 2B: Complete nutrient exclusion from duodenum increases fasting and glucose stimulated levels of GLP-1 to a greater extent compared to weight loss

Fasting levels of glucagon like peptide-1 (GLP-1) were increased in ELS-10 treated rats, and WMISO rats (figure 6A). WMISO rats exhibited an increased GLP-1 secretion in response to glucose, however this response was greater in ELS-10 rats (figure 6B).