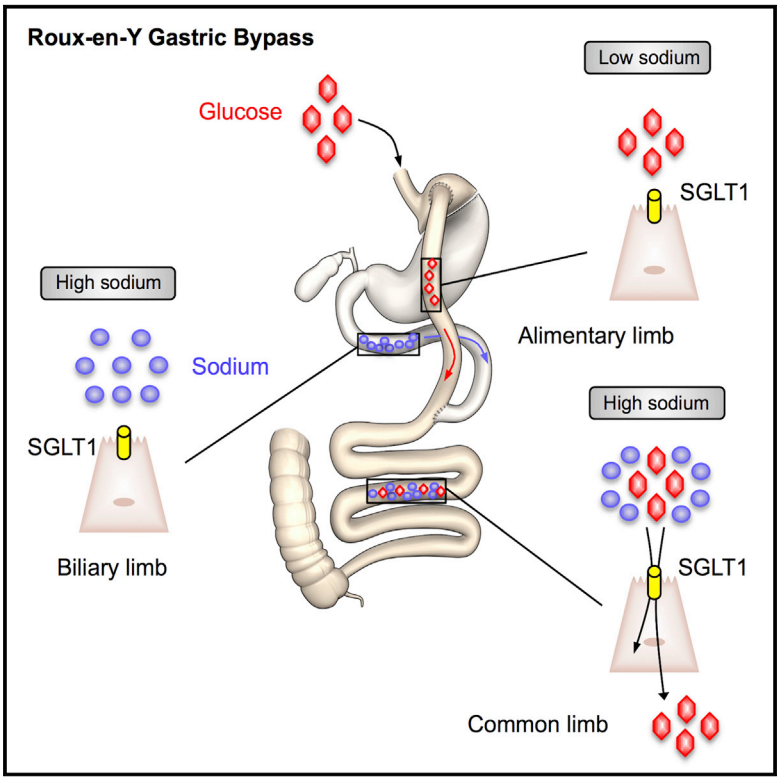
Short Article

Cell Metabolism

Bile Diversion in Roux-en-Y Gastric Bypass Modulates Sodium-Dependent Glucose Intestinal Uptake

Graphical Abstract



Highlights

- Glucose is absorbed only in the common limb in Roux-en-Y gastric bypass
- Sodium-glucose co-transport is blunted in the bile-deprived alimentary limb
- Sodium addition restores glucose uptake in the alimentary limb
- Roux-en-Y gastric bypass decreases postprandial glucose response in humans

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In Brief

The beneficial metabolic consequences of bariatric surgery independent of weight loss remain largely unexplained. Baud et al. identify sodium as a key factor and show that Roux-en-Y gastric bypass decreases the amount of sodium normally brought into the intestine with bile, thereby impairing intestinal glucose uptake via sodium-glucose cotransport.

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Bile Diversion in Roux-en-Y Gastric Bypass Modulates Sodium-Dependent Glucose Intestinal Uptake

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SUMMARY

Gastro-intestinal exclusion by Roux-en-Y gastric bypass (RYGB) improves glucose metabolism, independent of weight loss. Although changes in intestinal bile trafficking have been shown to play a role, the underlying mechanisms are unclear. We performed RYGB in minipigs and showed that the intestinal uptake of ingested glucose is blunted in the bile-deprived alimentary limb (AL). Glucose uptake in the AL was restored by the addition of bile, and this effect was abolished when active glucose intestinal transport was blocked with phlorizin. Sodium-glucose cotransporter 1 remained expressed in the AL, while intraluminal sodium content was markedly decreased. Adding sodium to the AL had the same effect as bile on glucose uptake. It also increased postprandial blood glucose response in conscious minipigs following RYGB. The decrease in intestinal uptake of glucose after RYGB was confirmed in humans. Our results demonstrate that bile diversion affects postprandial glucose metabolism by modulating sodium-glucose intestinal cotransport.

INTRODUCTION

Weight loss surgery is an efficient treatment for obesity and related metabolic diseases (Sjöström, 2013). In patients with type 2 diabetes (T2D), Roux-en-Y gastric bypass (RYGB), which excludes a portion of the stomach and the proximal intestine from the alimentary circuit, improves glucose metabolism more rapidly (Hickey et al., 1998) and to a greater extent than expected from weight loss alone (Laferrère et al., 2008). RYGB is also more efficient than exclusively restrictive operations to reverse nonalcoholic fatty liver disease (Caiazzo et al., 2014). These observations suggest that bypassing the foregut may directly contribute to improved glucose metabolism. One proposed mechanism is the exaggerated postprandial secretion of GLP-1 and the resulting improvement of beta cell function (Jørgensen et al., 2013). Some authors have also suggested that RYGB reduces the secretion of diabetogenic proteins by the duodenum (Rubino et al., 2006; Salinari et al., 2013) or modulates glucoregulatory nutrient sensing in the jejunum (Breen et al., 2012). Other studies incriminated glucose handling by the bile-deprived alimentary limb (AL). The proposed mechanisms include a functional defect in sodium-glucose intestinal cotransporter (Stearns et al., 2009), an increase in intestinal neoglucogenesis and portal glucose sensing (Troy et al., 2008), or an increase in enterocyte metabolism and GLUT1-mediated uptake of circulating glucose (Cavin et al., 2016; Saeidi et al., 2013). Interestingly, the main metabolic features of RYGB can be experimentally reproduced by diverting bile flux from the hepatic duct directly to the distal intestine (Kohli et al., 2013; Flynn et al., 2015; Goncalves et al., 2015). Here, we demonstrated that the exclusion of bile and other digestive fluids decreases active glucose intestinal uptake by disturbing the intestinal circulation of endogenous sodium and hence blunting the sodium microclimate in the AL, resulting in a decrease in postprandial blood glucose response.

RESULTS

Ingested Glucose Is Absorbed in the Common Limb

After RYGB, ingested food passes directly from a small gastric pouch to a jejunal segment called the alimentary limb (AL). Bile travels with other gastrointestinal fluids through the intact upper duodenojejunal segment, or biliary limb (BL), and only encounters nutrients in the distal portion of the intestine, or the common limb (CL). Our first aim was to identify the contribution of these different intestinal segments on postprandial glucose homeostasis in a clinically relevant model. Thus, we performed RYGB in adult minipigs (Verhaeghe et al., 2014) and measured blood glucose, plasma insulin, and GLP-1 concentrations during the progression of a mixed meal (MM) first in the AL and then in the CL (Figure 1A). Blood glucose concentrations slightly increased, although not significantly, when the meal was physically confined to the AL by the intestinal clamp and reached a steady state between 90 min and 180 min (Figure 1B). Conversely, blood glucose concentrations rapidly increased