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The role of foregut exclusion in the deterioration of glucose and lipid metabolism induced by a high-fat diet

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ABSTRACT

Aim: The small intestine may be involved in the improvement of glucose and lipid metabolism after bariatric surgery; however, the role of the foregut in metabolic changes remains unclear. This study used normal rats fed a high-fat diet (HFD) after bariatric surgery to determine the role of the foregut in glucose and lipid metabolism.

Methods: Duodenum–jejunum bypass (DJB), gastrojejunostomy (GJ) and sham-operations were performed on Sprague-Dawley (SD) rats. Oral glucose tolerance, insulin sensitivity, β-cell function, lipid profile, glucose-stimulated glucose-dependent insulinotropic polypeptide (GIP) levels and glucagon-like peptide-1 (GLP-1) levels were measured. The rats were observed for 24 weeks post-surgery.

Results: Food intake and body weight were similar between the groups during the study period ($P > 0.05$). The DJB group exhibited better glucose and lipid metabolism than the other groups ($P < 0.05$). Compared with the GJ group, the DJB group demonstrated superior oral glucose tolerance, insulin sensitivity and lipid profiles ($P < 0.05$); β-cell function in the two groups was similar ($P > 0.05$). The GIP levels were decreased in the DJB group and increased in the GJ group ($P < 0.05$), and the GLP-1 levels were increased in the DJB and GJ groups ($P > 0.05$).

Conclusions: We found that foregut exclusion can prevent disordered glucose and lipid metabolism. Additionally, decreased GIP secretion was associated with improvements in glucose tolerance and insulin sensitivity, particularly related to lipid metabolism. Increased GLP-1 benefited β-cell function; however, it could not reverse the disordered glucose and lipid metabolism induced by a HFD.

1. Introduction

Increasing evidence suggests that bariatric surgery improves glucose and lipid metabolism in patients with type 2 diabetes (T2DM) [1,2], although the mechanism by which T2DM rapidly improves after bariatric surgery has not been elucidated. Researchers hypothesize that alterations to the small intestine resulting from surgery might play an important role in T2DM remission, including the exclusion of the foregut (duodenum and proximal jejunum) from nutrient exposure and more rapid delivery of nutrients to the hindgut (distal ileum) [3–6].

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These alterations to the small intestine change the levels of the two major incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [7,8]. GIP is released from the enteroendocrine K cells concentrated in the duodenum and proximal jejunum in response to the absorption of nutrients and has been shown to stimulate insulin release and enhance β-cell growth, differentiation, proliferation and survival [9]. Additionally, GLP-1 is released from the enteroendocrine L cells concentrated in the distal ileum and colon in response to the absorption of nutrients. GLP-1 can enhance insulin secretion, stimulate β-cell proliferation and decrease β-cell apoptosis [10,11]. The effect of incretins on either glucose or lipid metabolism was shown to be impaired in T2DM patients [12].

A recent study showed that bariatric surgery appeared to be markedly more efficient than standard care in the prevention of T2DM in obese persons [13]. Based on previous studies [23,24], changes in glucose and lipid metabolism were observed after bariatric surgery, suggesting that bariatric surgery could prevent T2DM. We proposed that disorders of glucose and lipid metabolism might not occur in a normal animal model following bariatric surgery.

Considering that a long-term high-fat diet (HFD) could lead to glucose and lipid metabolism disorders, we fed a HFD to normal rats after bariatric surgery. We performed duodenum–jejunum bypass (DJB) and gastrojejunostomy (GJ) on normal Sprague-Dawley (SD) rats; these surgical procedures rapidly delivered nutrients to the hindgut. These procedures differed only in that the foregut was excluded in DJB. The rats were fed a HFD post-surgery, and the effect of DJB was compared to that of GJ to determine the roles of the foregut and hindgut on improvement in glucose and lipid metabolism.

2. Material and methods

2.1. Animals and HFD

Male SD rats, between 6 and 8 weeks of age, were purchased from the National Rodent Laboratory Animal Resources (Shanghai, China). Animals were fed water and a 5% fat rat chow diet (14% of the calories were from fat).

The rats were housed individually in an air-conditioned room at 22 ± 2 °C with a 12:12-h light–dark cycle (0800-2000). The study was approved by the Animal Care and Utilization Committee of Central South University.

2.2. Experimental protocol

After the rats were acclimated for 2 weeks, food intake, weight and oral glucose tolerance were measured. The rats were randomly grouped ($n = 20$) and subjected to one of the following procedures: DJB, GJ, sham-operation or no intervention (controls). After surgery, the rats in each group were fed a HFD diet (40% of the calories were from fat).

Weight and food intake following surgery were monitored and recorded. Oral glucose tolerance tests (OGTT) were performed at 2, 4, 12 and 24 weeks after surgery. Plasma lipids, insulin tolerance (ITT), glucose-stimulated insulin, C-peptide and GIP and GLP-1 secretions were measured at preoperative and postoperative weeks 2 and 24.

2.3. Interventions

The rats undergoing DJB/GJ or the sham operation were fasted overnight and anesthetized with 10% chloral hydrate.

DJB surgery was performed as previously described by Rubino et al. [5], and the gastric volume was maintained intact. The duodenum was transected at 0.5 cm from the pylorus, and the distal limb was closed using a 5–0 silk suture. A length of 10 cm from the ligament of Treitz in the distal jejunum was transected, and the distal limb was directly connected to the stomach (gastrojejunal anastomosis). The proximal limb carrying the biliopancreatic juices was reconnected downward to the alimentary limb at a distance of 10 cm from the gastrojejunal anastomosis. The DJB surgery delivered nutrients to the hindgut rapidly and excluded the foregut from nutrient exposure (Fig. 7A).

For GJ surgery, the gastric volume was maintained intact as in DJB. The prepyloric area of the stomach and the proximal portion of the jejunum were connected through a latero-lateral anastomosis. The site of the jejunum for the GJ anastomosis was at a distance of 10 cm from the ligament of Treitz as in DJB. GJ surgery delivered nutrients to the hindgut rapidly; however, the foregut nutrient passage was maintained (Fig. 7B).

The sham operations were performed in a manner similar to that of the non-sham surgeries as follows: transections of the gastrointestinal tract were performed at all the sites as in the DJB or GJ procedures, and anastomosis was also performed at the same sites.

After surgery, the rats had free access to drinking water, but food intake was restricted for 2 weeks.

2.4. Measurements

Weight and food intake were measured daily for the first 2 weeks after the intervention, followed by twice per week until the end of study

For the OGTT, the rats were fasted overnight, and the blood glucose was measured in conscious rats before (baseline) and 10, 30, 60, 120 and 180 min after the administration of 1 g/kg glucose by oral gavage. Blood samples were collected by tail snip and analyzed using a glucometer (One Touch® Ultra, Lifescan, Johnson & Johnson, Milpitas, CA, USA).

For the ITT, the fasting rats were treated with insulin (0.5 IU/kg) via intraperitoneal injection. Blood glucose levels were measured before and 30, 60, 120 and 180 min after insulin injection.

For the plasma hormone measurements, the rats were fasted overnight, and blood was collected from the tail at baseline and 15, 30, 60 and 120 min after oral glucose gavage. The blood was collected in EDTA tubes containing dipeptidyl peptidase-4 inhibitors, centrifuged (3000 rpm, 4 °C, 10 min), and the plasma was stored at −80 °C until analysis. Rat enzyme-linked immunosorbent assay kits (ELISA; R&D systems, Minneapolis, MN, USA) were used to assess serum levels of glucose-stimulated insulin, fasting C-peptide, GIP and GLP-1.

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