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Research Paper

Esophagus-duodenum Gastric Bypass Surgery Improves Glucose and Lipid Metabolism in Mice

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ABSTRACT

Background: Despite of its significant therapeutic effects on obesity and metabolic diseases, Roux-en-Y gastric bypass (RYGB) has limited clinical application because of considerable impacts on the gastrointestinal structure and postoperative complications. This study aims to develop a simplified surgical approach with less damage and complication but efficient metabolic benefit.
Methods: The effects of Esophagus-Duodenum gastric bypass (EDGB) on body weight, food intake, glucose and lipid metabolism were compared to RYGB in mice.
Findings: EDGB is simple, has higher survival rate and less complication. Relative to RYGB, EDGB demonstrated modest body weight control, identical improvement of glucose and lipid metabolism in obese mice. Blood glucose increased significantly 15 and 30 min after oral glucose administration, then markedly decreased in both EDGB and RYGB groups relative to the sham surgery, indicating a quicker absorption of oral glucose and improvement in glucose uptake by insulin targeted tissues. Insulin sensitivity was identically improved. EDGB significantly decreased plasma and hepatic triglyceride levels, while increased browning in visceral and subcutaneous white adipose tissue to the extent identical to RYGB. Levels of ghrelin and nesfatin-1 increased significantly after EDGB and RYGB.
Interpretation: EDGB is a valuable model to study the metabolic benefit of bariatric surgery in mice.

1. Introduction

Obesity and its associated morbidities such as Type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver diseases (NAFLD) impose a significant health burden worldwide. Conventional treatment of obesity and its associated chronic metabolic dysfunction is limited and often inefficient. Effective and long term management of obesity and T2DM remains a major challenge.

Bariatric surgery has demonstrated a significant efficacy in the treatment of obesity and T2DM. Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) are the most commonly performed bariatric surgeries (Debs et al., 2016; Haruta et al., 2017). RYGB is the most effective for durable treatment of T2DM imparting both weight loss dependent and independent improvement in glycemic control in 83.8% of morbidly obese patients (Buchwald et al., 2004). However, considerable alteration in structure and physiology of the gastrointestinal tract and adverse complications have significantly limited its application (Breznikar and Dinevski, 2009). Although infrequent, serious long-term complications may require reversal procedures. Bariatric surgery traditionally has been recommended for severely obese patients with a body mass index (BMI) of ≥40 kg/m^2 or for severely obese patients with BMI of ≥35 kg/m^2 with at least 1 co-morbid condition. More recently, the indications have been expanded to include obese patients with a BMI of 30 ≥ kg/m^2 and a metabolic condition, such as type 2 diabetes (Ponce et al., 2015; Brethauer, 2013).

Improvement in glycemic control after bariatric surgery can be either weight loss dependent and independent. RYGB often produces a massive weight reduction and a large extent in the improvement of glycemic control, but the improvement of glucose occurs before weight reduction. Weight loss after RYGB surgery, in particular in rodent model, occurs rapidly, with 20–30% weight lost within two weeks after surgery. This rapid weight loss makes it difficult to investigate the weight-loss-independent mechanisms for improvement of glucose homeostasis (Hao et al., 2013). Further, Asian patients are rarely "severely obese" because of differences in genetic background and diets. Interest in the mechanism independent of weight loss after bariatric surgery for patients with moderate obesity has thus been growing (Ezzati, 2016). An

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alternative bariatric surgery to replace RYGB is needed. VSG is rapidly gaining popularity with a trend to replace RYGB surgery because of its less damage and fewer complications. However, studies in mice have found that VSG is less effective for lasting reduction in body weight and improvement on glycemic control relative to RYGB, the gold standard surgery, in mice (Hao et al., 2017). Further, removal of majority of the stomach renders it impossible to reverse the procedure in case complications such as anemia and severe bone loss occur (Angrisani et al., 2015; Buchwald et al., 2004). These observations indicate that it is premature to replace RYGB with VSG surgery (Nguyen et al., 2016). For the gastroduodenal anastomosis (Billroth I) surgery, the antrum and pylorus are removed and the stomach is attached to the duodenum along its greater curvature. This bariatric surgery is performed much less often because its postoperative complications such as reflux gastritis and esophagitis are significantly higher than RYGB surgery (Zong and Chen, 2011). In this study, we presented a simplified bariatric surgery: Esophagus-Duodenum Gastric Bypass Surgery (EDGB) in mice. In this procedure, the 5% small gastric pouch is end-to-side connected to the duodenum, rendering food bypassing the stomach only. We compared the changes in food intake, body weight, glycemic control and lipid metabolism between the EDGB and RYGB surgeries in obese mice induced by high fat diet (HFD).

2. Materials and Methods

2.1. Animals

Four weeks-old C57BL/6 J mice weighted 16 ± 3 g were purchased and fed with a high-fat diet (45% fat, D12451; Research Diets, USA) for 12 weeks. At the time of surgery, obese mice were weight-matched and divided into Sham, EDGB and RYGB groups. Mice were fed with high-fat diet for 8 weeks after surgery until the end of experiments. All experiments were performed in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the Health Science Center of Peking University.

2.2. Surgical Procedures

Animals were fasted 4 to 6 h before operation and anesthetized with pentobarbital sodium (60 mg/kg body weight). Standard aseptic procedures were used throughout.

2.2.1. Roux-en-Y Gastric Bypass Surgery

We used the mouse RYGB model in which a pouch size of about 5% of the total stomach volume was created similar to typical RYGB surgery in humans. Briefly, mice were anesthetized and stomach exposed. Perigastric ligaments were ligated and cut to release the stomach. The left gastric vessel was separated bluntly from the cardia to make room for pouch operation without impairing the gastric blood supply. A titanium clip was applied to generate a small pouch size of about 5% of the total stomach volume. The stomach was transected right above the clip, leaving the left gastric vessels intact. Jejunum was transected about 2 cm distal to the ligament of Treitz. The small gastric pouch was then anastomosed to the cut end of the jejunum using 11-0 nylon suture in an uninterrupted suture fashion. For the jejuno-jejunostomy, a longitudinal slit was made on the anti-mesenteric side of the jejunum at 6 cm distal to the site of gastrojejunostomy, and the proximal end of the jejunum was joined in an end-to-side anastomosis using 11-0 nylon suture in an uninterrupted fashion. This resulted in a common limb consisting of the distal jejunum and the ileum of about 12 cm, a Roux limb about 5–6 cm and a biliopancreatic limb about 5–6 cm. In the abdominal wall, the muscular layer and skin were closed using interrupted 6-0 nylon suture and interrupted 5-0 nylon suture respectively (Hao et al., 2013).

2.2.2. Esophagus-Duodenum Gastric Bypass Surgery

After anesthesia, perigastric ligaments were ligated and cut to release the stomach and the small pouch size of about 5% of the total stomach volume was created using a titanium clip as described above in the RYGB procedure. The small gastric pouch was then sutured end-to-side to the duodenum bulb using 11-0 nylon suture in an uninterrupted fashion. Then the stomach and duodenum were put back in position. The abdominal cavity was closed with interrupted suture using 5-0 nylon suture.

2.2.3. Sham Surgery

For the sham operation, the stomach was released and the left gastric vessel separated from the cardia as described in RYGB and EDGB procedures. The stomach, esophagus, and small intestine were exposed and the abdominal cavity closed with interrupted suture.

2.2.4. Vagotomy

After anesthesia, perigastric ligaments were ligated and cut to release the stomach. The vagal nerves descending along the surface of the esophagus were traced, and the branch entering to the stomach was identified and cut, the branch to liver remained intake. The abdominal cavity was closed with suture as described above.

2.2.5. Postoperative Care

For the first 12 h after the operation, mice were placed on a heating pad set at 37 °C. Immediately after the surgery, mice were administrated subcutaneously with 0.7 ml of 5% dextrose and carprofen (5 mg/kg) for analgesia. Water and high-fat diet was made available after recovery from anesthesia. One day after surgery, mice were free to drink and fed with high-fat diet until euthanasia.

2.3. Measurement of Body Weight and Food Intake

Body weight was measured every week before and after surgery. Food intake was measured every 3 days after surgery. Spillage was weighted and subtracted.

2.4. Glucose Metabolism

Basal levels of glucose were measured using blood drawn from the tail vein 1 week before surgery and 8 weeks after surgery. For oral glucose tolerance tests (OGTT), mice were fasted for 16 h before gastric administration of glucose (3 g/kg body weight) by gavage. Blood was drawn from a cut at the tip of the tail at 0, 15, 30, 60, 90 and 120 min after glucose administration, and glucose concentrations were detected immediately. Area under the glucose curve (AUC) was calculated.

Intraperitoneal glucose tolerance tests (IPGTT) was also performed after intraperitoneal injection of glucose at a dose of 1.5 g/kg body weight.

For insulin tolerance tests (ITT), mice were fasted for 6 h, followed by intraperitoneal injection of insulin at a dose of 1 IU/kg body weight. Blood was drawn from a cut at the tip of the tail at 0, 15, 30, 60, 90 and 120 min for determination of glucose concentration.

2.5. Plasma Ghrelin and Nesfatin-1

Blood samples from mice were transcardially collected after anesthesia, immediately transferred to chilled polypropylene tubes containing EDTA-2Na (12.5 mg/ml) and aprotinin (1000 units/ml), and centrifuged at 1500g for 10 min at 4 °C. Plasma was separated and stored at −80 °C before use. Blood levels of total ghrelin were measured using an enzyme linked immunosorbent assay (ELISA). Acylated ghrelin was measured using radio immunoassay kit (Linco Bioscience Institute, St. Charles, MO) according to the manufacturer's instructions. Aprotinin was purchased from Amersham Biosciences (Pittsburgh, PA). Nesfatin-1

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