Eating Behavior and Glucagon-Like Peptide-1-Producing Cells in Interposed Ileum and Pancreatic Islets in Rats Subjected to Ileal Interposition Associated with Sleeve Gastrectomy

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Abstract

Background Ileal interposition–sleeve gastrectomy (II–SG) has been developed as a metabolic surgery based on the hindgut hypothesis. The aim of the present study was to test this hypothesis by studying the eating behavior, metabolic changes, and glucagon-like peptide-1 (GLP-1)–producing cells in rat models.

Methods Male Sprague–Dawley rats were subjected to laparotomy, II, SG, or II–SG. Eating behavior and metabolic parameters were monitored by an open-circuit indirect calorimeter designed for a comprehensive laboratory animal monitoring system. GLP-1–producing cells were examined by quantitative immunohistochemistry.

Results After II alone, satiety ratio, i.e., intermeal interval/meal size, was reduced, while calorie intake was increased at 2 and 6 weeks postoperatively. Respiratory exchange ratio, \( VCO_2/VO_2 \), was increased to above 1.0 (i.e., carbohydrate metabolism) during both daytime and nighttime at 2 weeks postoperatively. After SG alone, GLP-1–producing cells were increased in the pancreatic islets (in terms of volume density), but not in the ileum (number/mm). After II–SG, the rate of eating was reduced, while meal duration (min) was increased during both daytime and nighttime at 2 weeks postoperatively. GLP-1–producing cells were increased by about 2.5-fold in the interposed ileum and also increased to the same extent in the pancreatic islets as seen after SG alone. The increased GLP-1–producing cells in the pancreatic islets after SG or II–SG were located around the insulin-producing β cells.

Conclusions The present study provides evidence supporting the hindgut hypothesis. II–SG increased GLP-1 production both in the interposed ileum and in the pancreatic islets, leading to metabolic beneficial effects and altered eating behavior.

Keywords Food intake · GLP-1 · Ileal interposition · Ileum · Pancreatic islets · Sleeve gastrectomy · Energy expenditure · Respiratory exchange ratio

Introduction

Bariatric surgeries, such as Roux-en-Y gastric bypass, bilipancreatic diversion, or sleeve gastrectomy, exhibit a better therapeutic effect than conventional medical therapy on type 2 diabetes by mechanisms other than weight loss and/or reduced food intake [1–4]. The hindgut hypothesis has been proposed to explain the underlying mechanisms, i.e., early arrival of food in the hindgut suppresses gastrointestinal motility, gastric emptying, and small intestinal transit by neural as well as hormonal pathways, such as GLP-1 in the ileum [5–8]. According to this hypothesis, ileal interposition (II) with or without sleeve gastrectomy (SG) has been suggested as a novel method of metabolic surgery [1]. The aim of the present study was to test this hypothesis by studying the effects of II with or without SG on body weight, body composition, eating behavior, metabolic parameters, and GLP-1–producing cells. Anatomically correct surgical procedure in which only ileum was interposed and accurate determination of eating behavior using Comprehensive Laboratory Animal Monitoring System (CLAMS) were applied. GLP-1–producing cells in the ileum as well as the pancreatic islets were examined by quantitative immunohistochemistry.
Materials and Methods

Animals

Rats (Sprague-Dawley, male, adults) were purchased from Harlan™, Horst, The Netherlands. Males were used because female rats have food intake coinciding with ovarian hormones and males grow faster than females, making it easier to detect changes in body weight. The rats were housed in Makrolon Type-4 individually ventilated cages (four rats per cage) with regulated room temperature and humidity (22±2 °C, 50±10 %) and 12-h light/dark cycle. They had free access to tap water and standard rat pellet food (RM1 811004, Scanbur BK AS, Sweden). The study was approved by the Norwegian National Animal Research Authority (Forsøksdyrutvalget, FDU).

Experimental Design

The animals were divided into two groups: II (14 animals) and laparotomy (LAP) (six animals). In consideration of the “3Rs” for the human use of animals (i.e., reducing the number of animals while achieving the scientific purposes of the experiment) [9], rats in both groups were re-used and subjected to SG 7 weeks after the first operation. In addition, four non-operated normal rats were used as controls for immunohistochemical analysis of GLP-1.

The body weight was recorded regularly (three times/week) throughout the study period. Each rat was placed in the CLAMS cages five times and kept for 48 h at each time point for measurement of eating behavior and metabolic parameters (records from the second 24 h were used for data analysis). The five time points were 2 weeks before II or LAP, and 2 and 6 weeks after II/LAP, and 2 and 6 weeks after SG. At the same time points, the body composition was determined and fecal energy content was measured (for details, see the following discussion). At euthanization, tissue samples from ileum and pancreas were collected for analysis by immunohistochemistry.

Surgeries

Before all surgeries, the animals were fasted overnight but with free access to drinking water. Surgeries were performed under general anesthesia with isoflurane (4 % for induction, 2 % for maintenance). Atropin was given to SG rats at a dose of 0.04 mg/kg subcutaneously 20 min before anesthesia. Buprenorphine was injected subcutaneously (0.05 mg/kg) immediately after surgery in all animals and at 1 day postoperatively if needed. Physiological saline (0.9 % NaCl) was given subcutaneously at 10–15 mL after surgeries to keep the animals hydrated. Drinking water (but not food) ad libitum was started 4 h after the surgery and powdered food was provided on the next morning, until it was switched to ordinary pellet food on the 2nd postoperative day.

Ileal Interposition

II was performed through a midline abdominal incision. The ligament of Treitz was located, and the insertion location for the transposed ileum segment was marked approximately 3 cm distal to the ligament with saline-soaked gauze. The ileum segment (2.5–3.5 cm in length) with blood vessels at 0.5–1 cm proximal to the ileocecal valve was isolated and transected. Three anastomoses in an end-to-end fashion were made between cecum–distal jejunum, Treitz-side jejunum–proximal ileum, and distal ileum–jejunum (Fig. 1b, c). All anastomoses were performed in one layer with 6-0 absorbable sutures (Vicryl, Ethicon Inc., Sommerville, NJ, USA). The abdomen was closed in two layers using 4-0 absorbable sutures (Vicryl, Ethicon Inc., Sommerville, NJ, USA).

Sleeve Gastrectomy

SG was performed through a midline abdominal incision. The stomach was clamped along the greater curvature from the antrum to the rumen (forestomach) across the corpus (fundus), approximately 70 % of the stomach was removed, and then the stomach was closed in one layer with 6-0 absorbable sutures (Fig. 1b, c) [10]. The abdominal wall was closed in two layers with 4-0 absorbable sutures.

Laparotomy

LAP was performed by making a midline abdominal incision, locating the ligament of Treitz and ileum, and then closing the abdomen in two layers using 4-0 absorbable sutures.

Eating Behavior and Metabolic Parameters

Rats were placed in the cages of CLAMS (Columbus Instruments International, Columbus, OH, USA) with free access to standard rat powdered food (RM1 811004, total metabolizable energy of 2.57 kcal/g, Scanbur BK AS, Sweden) and tap water. This system is composed of a four-chamber open-circuit indirect calorimeter designed for continuous monitoring of individual rats. In order for rats to acclimate to this system, they were placed in these metabolic cages for 24 h before the first CLAMS monitoring. Food intake, feeding behavior, and metabolic parameters were recorded automatically. High-resolution feeding data were generated by monitoring all feeder balances every 0.5 s. The end of an eating