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Roux-en-Y gastric bypass augments the feeding responses evoked by gastrin-releasing peptides

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ABSTRACT

Background: Roux-en-Y gastric bypass (RYGB) is the most effective method for the treatment of obesity, and metabolic disease RYGB may reduce body weight by altering the feeding responses evoked by the short-term satiety peptides.

Materials and methods: Here, we measured meal size (MS, chow), intermeal interval (IMI) length, and satiety ratio (SR, IMI/MS; food consumed per a unit of time) by the small and the large forms of gastrin-releasing peptide (GRP) in rats, GRP-10 and GRP-29 (0, 0.1, 0.5 nmol/kg) infused in the celiac artery (CA, supplies stomach and upper duodenum) and the cranial mesenteric artery (CMA, supplies small and large intestine) in an RYGB rat model.

Results: GRP-10 reduced MS, prolonged the IMI, and increased the SR only in the RYGB group, whereas GRP-29 evoked these responses by both routes and in both groups.

Conclusions: The RYGB procedure augments the feeding responses evoked by exogenous GRP, possibly by decreasing total food intake, increasing latency to the first meal, decreasing number of meals or altering the sites of action regulating MS and IMI length by the two peptides.

Introduction

Roux-en-Y gastric bypass (RYGB) is the most effective method for the treatment of obesity and metabolic disease.[1,2] After this surgery, plasma levels of the orexigenic hormone ghrelin decrease, whereas plasma levels of the anorexigenic peptides glucagon-like peptide-1 (GLP-1) and peptide tyrosine tyrosine (PYY) increase.[3-6] Although these effects are thought to reduce appetite and improve glucose homeostasis, the extent to which these or other gut peptides are actually involved in RYGB remains in doubt. As such, the current work tested the hypothesis that a modified RYGB procedure, in which part of the stomach is removed, alters the feeding responses evoked by another anorexigenic peptide gastrin-releasing peptides (GRP), namely meal size (MS), intermeal interval (IMI) length, and satiety ratio (SR, IMI/MS, or amount of food consumed per a unit of time), and changes the gastrointestinal sites that regulate them. We have shown that GRP alters the previous feeding behaviors, that is, MS, IMI, and SR,[7-12] through sites supplied by the celiac artery (CA, supplies stomach, and upper duodenum).[13,14]

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This hypothesis is based on three facts. First, the primary source of GRP is the myenteric neurons of the stomach,[15-18] which are reduced in number and in size by the RYGB procedure. Second, the distribution of GRP receptors is in the distal stomach > distal duodenum > proximal stomach > colon = jejunum, esophagus, pylorus, proximal duodenum, ileum, rectum (Fig. 1).[9] RYGB changes the distribution of these receptors and the amount and type of chyme contacting them. Such changes may also alter the feeding responses evoked by the various satiety gut peptides such as exogenous and endogenous GRP. Third, the site of action regulating reduction of MS and prolongation of the IMI by GRP in normal rats resides in the area supplies by the CA, that is, stomach and upper duodenum.[13,14] However, because the RYGB surgery alters the architecture of the gastrointestinal tract, the site of action regulating these feeding responses by GRP may change.

The current work measured MS, IMI, and SR by exogenous GRP-10 and GRP-29, the small and the large form of GRP in the rat, respectively, and the gastrointestinal site of action regulating them in a modified RYGB rat model. Based on our earlier work in normal rats,[13,14] here, we tested two doses of GRP-10 and GRP-29, 0.1 and 0.5 nmol/kg, infused before the onset of the dark cycle in the CA and in the cranial mesenteric artery (CMA, supplies small and part of the large intestine) in near spontaneously free-feeding rats. Our findings suggest that indeed RYGB alters the feeding responses evoked by exogenous GRP and the sites of action regulating them in the rat.

Materials and methods

The Tuskegee University Animal Care and Use Committee approved the animal protocol for this experiment. Adult male

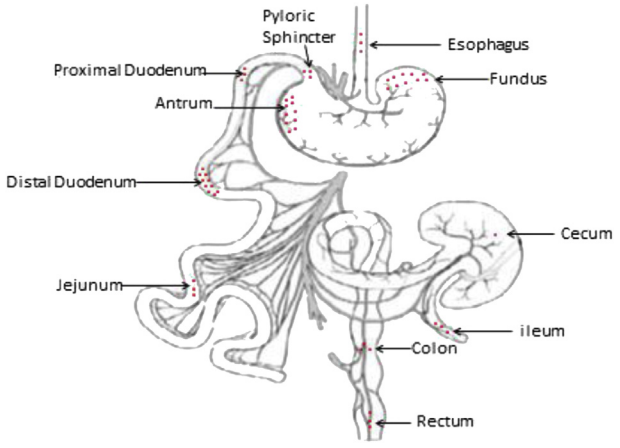

Fig. 1 – Distribution of gastrin-releasing peptide receptors. This schematic presentation indicates the distribution GRP in the gut. The highest secretion of GRP is shown to be primarily in the distal stomach, distal duodenum, proximal stomach, and intermediately secreted in the colon, moderately secreted in the jejunum esophagus, pyloric sphincter, proximal duodenum, ileum, and rectum (3 dots), and the lowest secretion was in the cecum. (Color version of figure is available online.)

Sprague Dawley rats weighing between 400-450 g ($n = 12$ sham and 16 RYGB divided equally into CA and CMA groups) were individually housed in the BioDAQ E2 system (Research Diets, New Brunswick, NJ) in a controlled environment (12-h dark/12-h light cycle—lights off at 1800 h, 21.5°C), with water and pelleted rodent chow (Teklad, Madison, WI) available *ad libitum*.

Surgical procedures

Modified RYGB

The procedure has been described previously[19] and is illustrated here in Figure 2. Briefly, after midline celiotomy, the jejunum was exposed and transected 40 cm distal to the pyloric sphincter. The fundus, the proximal upper third of the stomach, was removed, and the wall of the body of the stomach (the middle part of the stomach) was closed using a 5-0 PDS suture material. The antrum, the distal lower third of the stomach, was separated from the body of the stomach, and each compartment was closed using a 5-0 PDS suture material. An opening was created in the pouch formed by the closed body of the stomach, and the distal segment of the severed jejunum was anastomosed by an end-to-side anastomosis in the newly created gastric pouch using an 8-0 Ethilon suture material. The proximal end of the jejunum was anastomosed using an end-to-side anastomosis, with the jejunum at a point located 10 cm distal to the first transection point using a 7-0 vicryl suture material. This procedure created a 40-cm biliopancreatic limb and a 10-cm Roux, alimentary limb. Sham surgery was achieved by performing the same cuts and anastomosed back together without changing the architecture of the gastrointestinal tract.

Vascular catheterization

One catheter was implanted in each rat, as described previously.[13,14,20-22] Catheters (Micro-Renathane R-ITC-SP 9.5, Braintree Scientific, Braintree MA) were 24 cm long. The intravascular portion of the catheter was 0.25-mm OD × 0.12-mm ID, and the size of the remaining part was 0.84-mm OD × 0.36-mm ID. Catheterizations were performed using a surgical microscope (Carl Zeiss Opmi 160 12.5x/18B, 1 × 250, *Monument, CO*). General anesthesia, indicated by the absence of a pedal withdrawal reflex, was achieved with intramuscular injection of 1-mL/kg body weight of a mixture of 5.0 mL of Ketaset (100 mg/kg), 2.5 mL of Rompun (xylazine 20 mg/kg), Bayer, Shawnee Mission, KS, 1.0 mL of acepromazine maleate (10 mg/kg), Bayer, Shawnee Mission, KS, and 1.5 mL of saline. The abdominal wall was clipped and cleaned with three alternating betadine solution and alcohol swabs. A ventral midline celiotomy was performed.

The CA was exposed, and a temporary ligation was placed near the branch point from the aorta to prevent bleeding. The CA was punctured with a sterile 30-gage needle 1-2 mm distal to this ligature, and the catheter was threaded into the artery and fixed in place using cyanoacrylate glue. The temporary ligation was removed, and the catheter was threaded out of the abdominal cavity subcutaneously, exteriorized between the scapulae and secured with sutures and cyanoacrylate glue. The CMA was similarly catheterized. The femoral artery (FA) was exposed on the medial aspect of the right thigh, freed