A Pilot Study Examining the Effects of GLP-1 Receptor Blockade Using Exendin-(9,39) on Gastric Emptying and Caloric Intake in Subjects With and Without Bariatric Surgery

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Abstract

Background: Obesity causes significant morbidity and mortality and continues to be a significant public health concern. Unfortunately, lifestyle modification and pharmacotherapy do not produce durable results. This has led to bariatric surgical procedures playing an increasingly prominent role in the management of medically complicated obesity. Roux-en-Y gastric bypass and sleeve gastrectomy are the most commonly performed bariatric surgeries in North America and produce mechanical restriction with accelerated gastrointestinal transit accompanied by increased postprandial secretion of glucagon-like peptide-1 (GLP-1). GLP-1 is a gastrointestinal hormone that delays gastric emptying and causes satiety and weight loss. This raises the possibility that the postprandial rise in GLP-1 might affect feeding behavior over and above the mechanical restriction produced by bariatric surgery.

Methods: We, therefore, sought to determine the effects of GLP-1 receptor blockade using exendin-9,39—a competitive antagonist of the actions of GLP-1 at its receptor—on caloric intake and gastrointestinal transit in subjects after sleeve gastrectomy and after Roux-en-Y gastric bypass compared with weight-matched controls.

Results: GLP-1 receptor blockade did not alter caloric intake in people after bariatric surgery. However, caloric intake was decreased in age-, weight- and sex-matched control subjects, and the mechanisms require further study.

Conclusions: Given the known effects of GLP-1 on gastric accommodation, future studies should ascertain effects of GLP-1 receptor blockade on gastric accommodation, which might be a useful and novel strategy to decrease caloric intake in humans with an intact upper gastrointestinal tract. The Clinical Trial Registration number is NCT02779075.

Keywords: gastric emptying, gastric accommodation, caloric intake, incretin hormones, GLP-1 receptor

Introduction

IN THE UNITED STATES, the prevalence of obesity is rapidly increasing with 65% of adults and 17% of adolescents and children classified as being overweight or obese representing a doubling of obesity prevalence in adults, and a tripling in adolescents over the previous 25 years.¹ In 2008, national health care costs attributed to excess weight were estimated to be \$147 billion.^{2,3} More recently, estimates suggest that this figure may have doubled.⁴ Beha-

vioral intervention with lifestyle and dietary modification usually achieves modest weight loss.⁵ While generally safe, most people regain the weight lost within 5 years. Pharmacotherapy for obesity is considered for patients who have failed efforts at lifestyle modification and who have a body mass index (BMI) ≥ 30 kg/m² or a BMI ≥ 27 kg/m² in the presence of comorbidities, such as diabetes.⁶ However, there have been significant concerns about the long-term safety of such medications and the currently available medications have relatively limited efficacy.⁷ Bariatric surgery is

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usually considered for patients who have a BMI ≥ 40 kg/m² or a BMI ≥ 35 kg/m² associated with comorbidities such as diabetes.⁶ Observational studies suggest that bariatric surgery is the most effective intervention for weight loss producing an average weight loss of 30%–35%, that is, maintained in $\sim 60\%$ of patients at 5 years.⁸ This has led to a dramatic increase in the number of procedures performed annually.⁹

Both sleeve gastrectomy and Roux-en-Y gastric bypass increase glucagon-like peptide-1 (GLP-1) concentrations, which directly affect β cell function, although this is of lesser magnitude in sleeve gastrectomy compared with Roux-en-Y gastric bypass.^{10,11} It has been suggested that endogenous GLP-1 secretion may contribute to caloric intake over and above the mechanical restriction produced by bariatric surgery. GLP-1 and GLP-1 receptor agonists decrease food intake and cause weight loss.^{12,13} The attraction of certain foods may decrease after Roux-en-Y gastric bypass,¹⁴ consistent with the observation that GLP-1 also modulates taste sensitivity in rodents.^{15–18} These data suggest that appetite may be altered by enteroendocrine secretion.^{19,20} GLP-1 also alters gastrointestinal transit, gastric accommodation,^{11,21,22} and has direct effects on hypothalamic nuclei outside of the blood–brain barrier.²³ More recently, activation of the GLP-1 receptor decreased food intake and food-related brain responses in patients with type 2 diabetes and in obese subjects as measured by functional magnetic resonance imaging and these actions were blocked by exendin-9,39 (a known competitive antagonist of GLP-1²⁴). It is, therefore, reasonable to consider that the postprandial rise in GLP-1 might decrease caloric intake after Roux-en-Y gastric bypass, and to a lesser extent sleeve gastrectomy, where the increase in GLP-1 is less marked.^{25–29}

We, therefore, sought to determine the effects of GLP-1 Receptor blockade with exendin-9,39 on caloric intake and gastrointestinal symptoms in subjects after sleeve gastrectomy and after Roux-en-Y gastric bypass compared with weight-matched controls. We hypothesized that blockade of the GLP-1 receptor would increase caloric intake and decrease gastrointestinal symptoms in subjects after bariatric surgery. Subjects were studied on two occasions in random

order in the presence or absence of exendin-9,39. We report no effect of GLP-1 receptor blockade on caloric intake after bariatric surgery in contrast to lean controls.

Methods

Subjects

After approval by the Mayo Institutional Review Board, 9 weight-matched control subjects, 10 subjects after Roux-en-Y gastric bypass, and 6 subjects after sleeve gastrectomy gave informed, written consent to participate in the study. They had no history of diabetes or prediabetes. All subjects were at a stable weight and did not engage in regular vigorous exercise. Body composition was measured using dual-energy X-ray absorptiometry (DEXA scanner; Hologic, Waltham, MA) to determine lean body composition.

Experimental design

Participants were studied on two occasions in random order (Fig. 1). For each study, subjects were admitted to the Mayo Clinic Clinical Research and Translational Unit (CRTU) at 0600 on the morning of study after an overnight fast of 8 hr. At ~ 0615 (-210 min), a cannula was inserted into a hand vein to allow for infusion of saline or exendin-9,39. Before the study start at 0720 (-10 min) a Visual Analog Scale (VAS) was used to measure symptoms of nausea, fullness, bloating, and abdominal pain on the subjects. As before, the VAS for each of these symptoms consisted of a 100-mm horizontal line anchored with the words “none” and “worst ever” at the left and right ends of the lines.³⁰ At ~ 0730 (0 min) subjects consumed a meal consisting of one scrambled egg, 15 grams of ham, and Jell-O containing 35 grams of glucose. The meal is known to be tolerated by subjects who have had bariatric surgery. At this time (0 min), on the saline study day, an infusion of saline was started and continued until the end of the study. On the exendin-9,39 study day, at 0 min (0730), exendin-9,39 was infused @ 750 pmol/kg/min for 1 hr

FIG. 1. Experimental design.

(0–60 min). The rate of exendin-9,39 was then decreased to 300 pmol/kg/min for the next 3 hr (61–240 min). Subsequently, the rate was increased to 750 pmol/kg/min for the remainder of the study (241–300 min).

Free-choice caloric intake

At 1130 (240 min) there was a free-choice standard buffet to measure total caloric intake and macronutrient distribution in the chosen foods from standard foods of known nutrient composition: vegetable lasagna (Stouffers, Nestle USA, Inc., Solon, OH); vanilla pudding (Hunts, Kraft Foods North America, Tarrytown, NY); and skim milk. The amount of items eaten from the buffet (including partially consumed buffet items) was recorded over the subsequent hour. The total kilocalories of food consumed and macronutrients ingested were analyzed by validated software (ProNutra 3.0; Viocare Technologies, Inc., Princeton, NJ). The study ended at 1230 (300 min) when infusions (saline or exendin-9,39) were stopped, all cannulas removed, and subject left the CRTU.

Calculations and statistical analysis

In a prior experiment, we observed (mean $\pm$ standard deviation) free-choice caloric intake of 745 ± 86 kcal.³¹ Assuming similar variation, six subjects per group would provide 80% power (at a 2-sided 0.05 α level), to detect a 16% change in caloric intake in response to exendin-9,39. On the other hand, 10 subjects per group would provide similar power to detect a 12% change in caloric intake in response to exendin-9,39.

Data are presented as (observed) mean $\pm$ standard error of the mean. The analyses compared the within-group effect of treatment (exendin-9,39) with the data observed in the study, where saline is infused. This analysis used a paired *t*-test, or signed-rank test, as warranted. A *P* value <0.05 was considered to be statistically significant.

Results

Demographic characteristics

No significant differences in age, sex distribution and weight (as well as BMI) were observed in the three groups studied (Table 1).

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS

	Controls	Sleeve gastrectomy	Roux-en-Y gastric bypass	P ^a
N	9	6	10	
Time elapsed since bariatric surgery (years)	N/A	2.0 $\pm$ 0.6	4.0 $\pm$ 0.9	
Sex (M/F)	1/8	0/6	1/9	
Age (years)	44 $\pm$ 4	51 $\pm$ 3	44 $\pm$ 4	0.39
Weight (kg)	88 $\pm$ 7	81 $\pm$ 5	92 $\pm$ 7	0.58
BMI (kg/m ²)	30.6 $\pm$ 1.8	30.3 $\pm$ 1.8	32.6 $\pm$ 2.5	0.71
Lean body mass	49.1 $\pm$ 5.3	41.5 $\pm$ 2.1	50.9 $\pm$ 2.1	0.28

^aResults of one-way ANOVA.

ANOVA, analysis of variance; BMI, body mass index; N/A, not applicable.

Aggregate symptom scores

Exendin-9,39 infusion did not alter aggregate symptom scores over the course of the 4 hr after ingestion of the initial test meal in subjects who had not undergone bariatric surgery (Panel A) (Fig. 2). Similarly, there was no effect on gastrointestinal symptoms during the course of the free-choice buffet.

Similarly, exendin-9,39 did not alter symptoms in subjects with sleeve gastrectomy after ingestion of the test meal (Panel B). On the other hand, during the free-choice buffet meal, exendin-9,39 increased symptoms in the first 30 min (93 ± 9 vs. 41 ± 12 mm, $P=0.03$) although this effect was attenuated by the end of the study (69 ± 9 vs. 54 ± 14 mm, $P=0.46$). No significant effect of exendin-9,39 on gastrointestinal symptoms was observed in subjects after Roux-en-Y gastric bypass (Panel C).

Free-choice caloric intake

Exendin-9,39 infusion decreased carbohydrate consumption (379 ± 60 vs. 459 ± 54 kcal, $P<0.01$) in control subjects (Panel A) (Fig. 3). In contrast, although carbohydrate consumption was lower, exendin-9,39 did not alter carbohydrate intake after sleeve gastrectomy (154 ± 21 vs. 158 ± 23 kcal, $P=0.74$) or Roux-en-Y gastric bypass (209 ± 14 vs. 211 ± 21 kcal, $P=0.91$).

Exendin-9,39 infusion also resulted in a modest, but significant, decrease in protein consumption (154 ± 28 vs. 179 ± 23 kcal, $P=0.04$) in control subjects (Panel B). As was the case for carbohydrate consumption, exendin-9,39 did not alter protein consumption after sleeve gastrectomy or Roux-en-Y gastric bypass.

A similar pattern for fat consumption was observed with a small, but significant, effect on fat consumption in control subjects (Panel C— 147 ± 23 vs. 182 ± 20 kcal, $P=0.03$). Fat consumption was unaffected by exendin-9,39 in people with sleeve gastrectomy or Roux-en-Y gastric bypass.

Discussion

Blockade of the GLP-1 receptor in people with a Roux-en-Y gastric bypass did not significantly alter gastrointestinal symptoms or free-choice caloric intake. This would imply that the elevated peripheral concentrations of GLP-1 seen in the postprandial period after this form of bariatric surgery do not alter upper gastrointestinal function and food consumption (at least of the food choices used). In people after sleeve gastrectomy similar results were observed—although there was a slight but significant increase in gastrointestinal symptoms during the buffet meal. Paradoxically, symptoms were increased by GLP-1 blockade (the opposite of what was hypothesized) but caloric intake was unaffected. Taken together, these changes imply that mechanical factors alter ingestive behavior to a greater extent after bariatric surgery than does postprandial secretion of GLP-1.

Restrictive forms of bariatric surgery decrease stomach capacity and accelerate gastric emptying. This results in rapid delivery of nutrients to the proximal (and distal) small intestine stimulating a significant increase in GLP-1 secretion. This rise is most marked after Roux-en-Y gastric bypass but sleeve gastrectomy is also associated with a rise in GLP-1.^{10,11} Selective antagonism of the GLP-1 receptor

FIG. 2. Aggregate gastrointestinal symptom scores in control subjects (**A**), people after sleeve gastrectomy (**B**) and people after Roux-en-Y gastric bypass (**C**) in the presence and absence of exendin-9,39 during the course of the experiment.

with a competitive antagonist of GLP-1 at its cognate receptor—exendin-9,39—has shown that this endogenous GLP-1 secretion directly stimulates β cell function and delays gastric emptying of solids.¹¹ GLP-1 also has direct effects on hypothalamic nuclei outside of the blood–brain barrier.²³ GLP-1 and GLP-1 receptor agonists decrease food intake and cause weight loss.^{12,13} GLP-1 also modulates taste sensitivity in rodents.^{15–18}

Inhibition of GLP-1 action with exendin-9,39 after Roux-en-Y gastric bypass accelerates gastric emptying.¹¹ The attraction of certain foods decreases after Roux-en-Y gastric bypass¹⁴ and appetite may be altered by enteroendocrine secretion.^{11,19} Taken together these observations suggest that factors other than anatomy could regulate the upper gastrointestinal response to food ingestion especially after bariatric surgery. In fact, the peripheral concentrations of GLP-1, observed in the early postprandial period in subjects post Roux-en-Y gastric bypass, exceed concentrations observed when GLP-1 is infused at 0.75 pmol/kg/min and are similar to those observed during GLP-1 infusion at 1.5 pmol/kg/min—both rates that are known to alter gastrointestinal motility and induce anorexia, bloating, and nausea.³² It is, therefore, reasonable to consider that the

postprandial rise in GLP-1 might affect feeding behavior after Roux-en-Y gastric bypass, and to a lesser extent SG, where the increase in GLP-1 is less marked.^{25–29} The literature in this regard has been mixed with some studies suggesting that endogenous GLP-1 alters ingestive behavior^{24,33} while others failed to observe significant effects.³⁴

This pilot study was intended to determine primarily if blockade of the GLP-1 receptor increased caloric intake in subjects after bariatric surgery—presumably by decreasing central GLP-1 signaling. In addition, we sought to determine if GLP-1 alters upper gastrointestinal symptoms after meal ingestion. We, therefore, studied subjects with and without bariatric surgery using a standardized test meal and VASs to measure aggregate gastrointestinal symptoms (nausea, fullness, bloating, and abdominal pain) for the 4 hr after ingestion of this meal. In addition, subjects were then presented with a free-choice buffet meal to determine their caloric intake and gastrointestinal symptoms in the presence and absence of GLP-1 receptor blockade. The infusion rate of exendin-9,39 was modified to ensure adequate blockade even at peak postprandial concentrations of GLP-1.

It is notable that despite a smaller gastric pouch after Roux-en-Y gastric bypass, free-choice caloric intake was

FIG. 3. Free-choice caloric intake of carbohydrate (A), protein (B), and fat (C) in control subjects, people after sleeve gastrectomy and people after Roux-en-Y gastric bypass in the presence and absence of Exendin-9,39.

greater than in subjects after sleeve gastrectomy (267 ± 37 vs. 353 ± 21 kcal, $P=0.05$ sleeve gastrectomy vs. Roux-en-Y gastric bypass, respectively). There is some evidence that the volume of the gastric pouch/remnant increases in size over time—perhaps as a consequence of dysfunctional eating—which leads to loss of efficacy of the procedure and

explain the greater caloric intake in this group compared with subjects after sleeve gastrectomy.³⁵

It is possible that GLP-1 receptor blockade after bariatric surgery might produce compensatory changes in the secretion of other enteral hormones with opposite effects on ingestive behavior, whether directly or through subtle alterations in gut motility. For example, Svane et al. reported an increase in PYY₃₋₃₆ secretion during exendin-9,39 infusion after RYGB.³³ Since PYY₃₋₃₆ (which decreases appetite) is generated from intact PYY by the actions of dipeptidyl-peptidase-4 (DPP-4), use of a DPP-4 inhibitor with exendin-9,39 was able to increase food intake in these experiments. Indeed, this mechanism might explain the neutral effect of DPP-4 inhibitors on food intake.³¹

Another potential reason for a failure to detect an effect of exendin-9,39 on *ad lib* food intake is a lack of power. However, given the variation observed in subjects after RYGB, for example, we had 80% power to detect a 66 kcal change (18%) in food intake induced by exendin-9,39 infusion.

More surprisingly, GLP-1 receptor blockade with exendin-9,39 decreased caloric intake in matched subjects without bariatric surgery. Multiple factors influence satiation, including gastric volume. The stomach increases in volume in anticipation of, and after, food ingestion—a process referred to as gastric accommodation.³⁶ In the normal stomach, this expansion is not associated with an increase in gastric wall stiffness suggesting a change in stomach wall compliance to accommodate the capacitive function of the stomach.³⁷ We³⁷ and others^{38,39} have shown that GLP-1 increases gastric accommodation and compliance through vagal signaling.²¹ It is, therefore, possible that the decrease in stomach compliance (and consequent increase in wall tension) accompanying GLP-1 receptor blockade may explain the equivalent degree of upper gastrointestinal symptoms observed despite a decrease in caloric intake during the free-choice buffet meal.

In conclusion, this series of experiments refuted our hypothesis that the postprandial rise in GLP-1 concentrations associated with bariatric surgery might restrain nutrient intake and increase postprandial symptoms. Whether this is due to a lack of effect of GLP-1 after bariatric surgery, or because of compensatory mechanisms extant only after bariatric surgery remains to be ascertained. However, in age-, weight-, and sex-matched subjects without prior upper gastrointestinal surgery, we hypothesize that inhibition of GLP-1-mediated gastric accommodation could explain the decrease in caloric intake observed during GLP-1 receptor blockade. It remains to be ascertained whether similar interventions might be viable therapies for obesity by decreasing caloric intake in obese individuals with an intact upper gastrointestinal tract.

Author Disclosure Statement

No competing financial interests exist.

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