OBJECTIVE—Gastric bypass (GB) surgery is associated with postprandial hyperinsulinemia, and this effect is accentuated in postsurgical patients who develop recurrent hypoglycemia. Plasma levels of the incretin glucagon-like peptide 1 (GLP-1) are dramatically increased after GB, suggesting that its action contributes to alteration in postprandial glucose regulation. The aim of this study was to establish the role of GLP-1 on insulin secretion in patients with GB.

RESEARCH DESIGN AND METHODS—Twelve asymptomatic individuals with previous GB (Asym-GB), 10 matched healthy nonoperated control subjects, and 12 patients with recurrent hypoglycemia after GB (Hypo-GB) had pre- and postprandial hormone levels and insulin secretion rates (ISR) measured during a hyperglycemic clamp with either GLP-1 receptor blockade with exendin-(9–39) or saline.

RESULTS—Blocking the action of GLP-1 suppressed postprandial ISR to a larger extent in Asym-GB individuals versus control subjects (33 ± 4 vs. 16 ± 5% P = 0.04). In Hypo-GB patients, GLP-1 accounted for 43 ± 4% of postprandial ISR, which was not significantly higher than that in Asym-GB subjects (P = 0.20). Glucagon was suppressed similarly by hyperglycemia in all groups but rose significantly after the meal in surgical individuals but remained suppressed in nonsurgical subjects. GLP-1 receptor blockade increased postprandial glucagon in both surgical groups.

CONCLUSIONS—Increased GLP-1–stimulated insulin secretion contributes significantly to hyperinsulinism in GB subjects. However, the exaggerated effect of GLP-1 on postprandial insulin secretion in surgical subjects is not significantly different in those with and without recurrent hypoglycemia. Diabetes 60:2308–2314, 2011

Surgery to induce weight loss has become increasingly common (1) as obesity has become pandemic (2). Roux-en-Y gastric bypass (GB), which is associated with substantial and durable weight loss (3), has been reported to cause near complete remission of diabetes within days—before any significant weight loss (4,5). The mechanisms for these metabolic benefits independent of weight loss are still unknown, but it is clear that the insulin response to meal ingestion is exaggerated after surgery (6). Postprandial insulin secretion is augmented by the actions of hormones released from the gastrointestinal (GI) tract, primarily glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (7), and GB subjects have elevated plasma concentrations of GLP-1 (6,8–13). These findings are the basis for a popular but as yet unproven hypothesis that increased GLP-1 secretion is responsible for the improvement in glucose regulation following GB.

Moreover, in recent years there have been increasing reports of severe hyperinsulinemic hypoglycemia occurring in patients several years after GB (14,15). Affected individuals have exaggerated insulin and GLP-1 responses to meal consumption compared with asymptomatic individuals with GB (16). These observations raise the question as to whether an amplified GLP-1 effect, either from higher plasma levels or increased sensitivity to the peptide, accounts for the syndrome of post-GB hypoglycemia.

In the current study, exendin-(9–39) (Ex-9), a specific GLP-1 receptor (GLP-1r) antagonist (17), was used to test the hypothesis that GB–associated hyperinsulinemia is mediated by increased GLP-1 action and to determine whether enhanced GLP-1 action accounts for greater β-cell stimulation in subjects with postsurgical hypoglycemia.

RESEARCH DESIGN AND METHODS

Twelve asymptomatic subjects with previous GB (Asym-GB) and 10 control subjects with normal glucose tolerance and no prior GI surgery were recruited. Twelve patients with recurrent hypoglycemia following GB (Hypo-GB) based on their clinical symptomatology also participated. The hypoglycemic group was defined by recurrent events that included the presence of Whipple’s triad (capillary blood glucose level <2.8 mmol/L associated with hypoglycemic symptoms that resolved with carbohydrate ingestion) (18). Ten of the Hypo-GB subjects had clinically severe hypoglycemia marked by a progression from adrenergic symptoms (tremor, pallor, sweating, anxiety, palpitations, hunger, and weakness) to neuroglycopenic symptoms (cognitive dysfunction, loss of consciousness, and/or seizure) over the period of 1–2 years before they were studied. None of the Asym-GB subjects reported any hypoglycemic symptoms after surgery, whereas Hypo-GB subjects develop postprandial hypoglycemic symptoms (adrenergic symptoms) 2–5 years after their surgery. Three subjects each from the Asym-GB and Hypo-GB groups had a history of type 2 diabetes with no known complications that was controlled with diet or oral antidiabetic medications preoperatively and resolved completely after surgery.

The three groups had similar BMI, age, and sex distribution, and had stable body weight for at least a month before study. Asym-GB and Hypo-GB subjects had similar total weight loss and time since surgery, even though Hypo-GB subjects had a larger weight loss in the 1st year after surgery (P = 0.01) and consequently larger weight gain prior to their recruitment compared with Asym-GB subjects (Table 1).

The studies were approved by the institutional review board of the University of Cincinnati, and all participants provided written informed consent prior to the studies.

Peptides. Synthetic exendin-(9–39) (Ex-9) (C S Bio, Menlo Park, CA) was greater than 95% pure, sterile and free of pyrogens. Lyophilized Ex-9 was dissolved in 0.25% human serum albumin and dispensed by the Research Pharmacy at Cincinnati Children’s Hospital. The use of synthetic Ex-9 is approved under the U.S. Food and Drug Administration IND 65837.
Experimental protocols. Subjects were instructed to maintain normal carbohydrate ingestion for 3 days before each visit, and not to engage in more than usual physical activity. None of the subjects were taking medication known to affect glucose metabolism. Participants were admitted to the General Clinical Research Center at Cincinnati Children’s Hospital after an overnight fast. All surgical subjects except for one patient from the Hypo-GB group had a screening meal tolerance test (MTT). All subjects had paired MTT-hyperglycemic clamps (MTT-clamp) that were separated by an interval of at least 1 week. Blood was sampled through an intravenous (IV) catheter in an antecubital vein and the arm continuously warmed to arterialized venous blood.

**MTT.** After removal of fasting blood samples, surgical subjects consumed a 25% ml liquid mixed meal containing 350 kcal with a calorie distribution of 57% carbohydrate, 15% protein, and 28% fat (Ensure Plus, Abbott Laboratories, Abbott Park, IL) within 10 min and blood samples were drawn from 0–180 min. Studies were terminated if subjects had hypoglycemic symptoms associated with blood glucose <2.8 mmol/L (Fig. 1).

**MTT-clamp.** After removal of fasting blood samples, a primed continuous infusion of 25% glucose was started at time 0 to achieve and maintain a target blood glucose concentration 8–9 mmol/L above fasting levels. At 30 min, subjects received either 1) an IV bolus of Ex-9 (7,500 pmol/kg) over 1 min followed by a continuous infusion (750 pmol/kg/min) for the remainder of the study, or 2) saline as a control (19,20). The order of the infusions was balanced so that half the subjects received saline first and half Ex-9 first. At 90 min, subjects consumed a liquid mixed meal (Ensure Plus), including 12 g of D-xylose, within 60 min. The rate of IV glucose infusion was adjusted to maintain the blood glucose at the target level throughout the study. Blood samples were drawn at scheduled intervals from 0–270 min, and plasma was separated within 60 min for storage at –80°C until assayed.

**Assays.** Blood samples were collected in tubes containing heparin for determinations of insulin, D-xylose, and glucose, and in tubes containing 50 mmol/L EDTA plus 50 kallikrein inhibitory units/ml, aprotinin for measurement of GLP-1, GIP, C-peptide, and glucagon. Blood glucose concentrations were determined at the bedside using an automated glucose analyzer (YSI 2300 STAT Plus, Yellow Springs Instruments, Yellow Springs, OH). Insulin was measured by radioimmunoassay using a double-antibody method of separating bound from free peptide. The sensitivity of this assay is 2 pmol/L, with intra- and interassay coefficients of variation of 5 and 7%, respectively, and proinsulin is recognized equally to insulin. Glucagon, total GLP-1, and C-peptide were measured using commercial radioimmunoassay kits according to the manufacturer’s specifications (Millipore Life Sciences, Billerica, MA). Addition of oxymorphone to the glucagon radioimmunoassay demonstrated cross-reactivity of <0.1%. D-xylose was measured by colorimetric assay (21). Total GIP was measured by ELISA using a method that recognizes both intact and metabolized peptide (Millipore Life Sciences, Billerica, MA).

**Calculations and analysis.** The mean of the three samples drawn at and before time 0 represented fasting levels of glucose and hormones. Insulin secretion rates (ISR) were derived from plasma C-peptide concentrations using deconvolution with population estimates of C-peptide clearance (19,22); an assumption underlying this analysis is that Roux-en-Y GB does not affect C-peptide kinetics. **MTT.** The insulinogenic index was calculated as the ratio of incremental insulin to incremental glucose concentration at 30 min after ingestion.

**MTT-clamp.** The stability of the hyperglycemic clamps was computed as the mean of coefficients of variation for each study from 60–270 min. The comparability of the paired clamps in each individual was computed as the difference in mean glucose from 60–270 min (19,20).

The β-cell response to IV hyperglycemia alone was computed as the relative increase in ISR from time 60–90 min compared with the fasting values.

The contribution of factors stimulated by meal ingestion on insulin secretion was calculated for each individual in the saline studies (where AUC is area under the curve) as: 100 × (ISR(60–270) – ISR(0–60))/ISR(0–60), where ISR(0–60) = Incremental AUCISR(60–270) during studies with saline over baseline and ISR(60–270) = Incremental AUCISR(60–270) during studies with saline over baseline.

The endogenous GLP-1 contribution to postprandial insulin secretion (GLP-1 effect) was calculated for each individual as: 100 × (ISR(60–270) – Ex-Sal(60–270))/ISR(0–60), where Ex-Sal(60–270) = Incremental AUCISR(60–270) during studies with Ex-9 over baseline.

The computations were also performed for the time period from 95–150 min. GLP-1, GIP, and D-xylose values from 0–90 min were taken as the preprandial baseline, and values following meal ingestion (GLP-1: 95–210, GIP: 95–240, and D-xylose: 95–130 min) were used to compute incremental postprandial AUC over baseline.

Glucagon response to IV hyperglycemia and meal ingestion was calculated as incremental AUC of glucagon levels from before (85–90 min) and after meal ingestion (95–270 min and 95–150 min) over baseline.

**Statistical analysis.** Data are presented as means ± SEM. The parameters obtained from each subject in studies with and without Ex-9 were compared among groups using two-way repeated-measures ANOVA. Baseline measures, parameters determined during the MTT, relative enhancement in ISR during saline hyperglycemic clamp studies, and endogenous GLP-1 contribution to insulin secretion were compared using ANOVA.

### RESULTS

**MTT.** Fasting blood glucose and insulin levels were comparable in Asym-GB and Hypo-GB groups. Following ingestion of the test meal, blood glucose fell to <2.8 mmol/L in 9 of 11 hypoglycemic subjects, who became symptomatic, within 60–150 min; 2 of 12 asymptomatic subjects had a glucose level <2.8 mmol/L within 100–120 min but without associated symptoms of hypoglycemia (Supplementary Fig. 1). The average peak glucose values after meal ingestion did not differ between the two groups (Asym-GB: 9.8 ± 0.4 mmol/L and Hypo-GB: 9.2 ± 0.5 mmol/L) (Fig. 1), although the mean nadir was significantly lower in the Hypo-GB subjects (Asym-GB: 3.5 ± 0.3 mmol/L and Hypo-GB: 2.3 ± 0.3 mmol/L; **P < 0.001**); because the studies were stopped in patients who became symptomatically hypoglycemic, the depth of the glucose nadir may have been underestimated in the Hypo-GB group. The Hypo-GB subjects had an earlier glucose drop (time to reach nadir glucose level during MTT, Asym-GB 128 ± 43 min vs. Hypo-GB 95 ± 30 min; **P = 0.045**) and a greater β-cell response immediately after meal ingestion compared with the Asym-GB group (insulinogenic index. Asym-GB: 195 ± 28 [pmol insulin]/[mmol glucose] vs. Hypo-GB: 455 ± 100 [pmol insulin]/[mmol glucose]; **P < 0.02**) (Fig. 1).

**MTT-clamp.** Fasting glucose and insulin levels were not different among the Asym-GB, Hypo-GB, and control groups or between the paired studies with saline or Ex-9 in each group.
studies, enteral factors accounted for 70 ± 2, 73 ± 4, and 55 ± 5% of insulin secretion from 95–270 min in the Asym-GB, Hypo-GB, and control subjects, respectively (Asym-GB vs. control, P = 0.01; Hypo-GB vs. control, P = 0.003). The higher contribution of enteral factors to insulin secretion in the GB subjects was especially evident in the 1st h after eating (80 ± 1% in Asym-GB and 81 ± 3% in Hypo-GB vs. 53 ± 7% in control subjects; P < 0.001 for pairwise comparison).

Also, insulin response to meal ingestion had a distinct pattern of rapid and accentuated peak in surgical patients compared with control subjects with no significant difference between the Asym-GB and Hypo-GB groups (6,288 ± 3,528 and 7,364 ± 4,439 pmol/L in Asym-GB and Hypo-GB subjects, respectively; P = 1.0).

Blocking GLP-1r suppressed postprandial insulin secretion significantly more in the GB groups (Asym-GB: 33 ± 4% and Hypo-GB: 43 ± 4%) than in the control subjects (16 ± 5%) (Asym-GB vs. control, P = 0.04; Hypo-GB vs. control, P = 0.002; Asym-GB vs. Hypo-GB, P = 0.20), and the magnitude of this effect was stable and persistent from 95–270 min (Fig. 2).

Fasting glucagon concentrations did not differ within the three groups or between the saline and Ex-9 studies (Table 2; Fig. 3). In the control subjects, glucagon decreased from fasting levels in response to IV hyperglycemia (60–90 min) during both the saline and Ex-9 studies and remained suppressed throughout the prandial portion of both clamp studies (Table 2, Fig. 3). In the surgical groups there was a similar reduction of plasma glucagon in response to the hyperglycemic clamp (Table 2). However, meal ingestion resulted in a substantial rise in plasma glucagon over preprandial values, and this response was greater when the action of endogenous GLP-1 was blocked particularly in the 1st h after meal ingestion (Table 2, Fig. 3).

Postprandial plasma D-xylose levels were significantly higher in surgical groups compared with nonsurgical control subjects; but infusion of Ex-9 had minimal effects on the passage of D-xylose from stomach or gastric pouch to the intestine (AUCD-xylose (90–130 min); saline, GB: 17.3 ± 3.9 vs. control: 3.4 ± 0.4 mmol/L·min; Ex-9, GB: 18.0 ± 3.5 vs. control: 4.1 ± 0.9 mmol/L·min; P = 0.03 for pairwise comparison) (Supplementary Figs. 2 and 3).

Fasting GLP-1 levels were comparable among the three groups and between the two studies. The plasma GLP-1 response to meal ingestion was significantly larger in GB subjects compared with control subjects, and was higher in the Hypo-GB than Asym-GB subjects (Table 2, Fig. 3). Ex-9 infusion significantly increased GLP-1 in response to food intake in all three groups (Table 2, Fig. 3). Meal consumption also increased plasma GIP concentrations in all three groups, but with an earlier peak in the GB surgical subjects (Table 2, Fig. 3). Blocking endogenous GLP-1 had no effect on GIP secretion (Table 2, Fig. 3).

FIG. 1. Blood glucose (C), insulin (B), and insulin secretion rate (A) in response to liquid meal ingestion at screening visit of Asym-GB (n = 12, solid line, closed symbols) vs. Hypo-GB (n = 11, dashed line, open symbols). Data are shown for the number of subjects at any given time as means ± SEM (only 2 of 11 subjects from Hypo-GB group completed the study).

Individual (Table 2, Fig. 2). Blood glucose concentrations were raised to the target level of hyperglycemia in each group (Table 2, Fig. 2), and were maintained comparably during the duration of the saline and Ex-9 studies (60–270 min). The average coefficient of variation of the glucose concentrations from 60–270 min during the saline clamps was 4.4 ± 0.3, 5.2 ± 0.4, and 4.7 ± 0.8% for Asym-GB, Hypo-GB, and control groups, respectively.

During the saline studies, insulin secretion rates rose by sixfold in response to IV glucose (60–90 min) and did not differ among the three groups (Table 2). The ratio of glucose infusion rates to plasma insulin levels during 60–90 min was not significantly different among the groups (3.3 ± 0.8, 3.3 ± 0.5, and 2.5 ± 0.5 mg/(kg·min) per pmol/L × 100 for Asym-GB, Hypo-GB, and control groups, respectively; P = 0.63) suggesting similar degrees of insulin sensitivity. Infusion of Ex-9 reduced insulin secretion during fasting hyperglycemia (60–90 min) by 18 ± 7, 20 ± 5, and 18 ± 10% in the Asym-GB, Hypo-GB, and control groups, respectively (P < 0.001 vs. the matched saline study) (Table 2).

In all three groups, meal ingestion augmented β-cell secretion (95–270 min) over premeal values (60–90 min) during both saline and Ex-9 studies (Table 2, Fig. 2). During saline
Effect of meal ingestion during hyperglycemic clamp on islet hormonal response and GI peptides in studies with and without IV Ex-9 infusion in Asym-GB, Hypo-GB, and nonsurgical control subjects

| Treatment | Asym-GB | Hypo-GB | Control Subjects |
|-----------|---------|---------|------------------|
| Glucose (mmol/L) Fasting | 4.5 | 4.5 | 4.5 |
| Glucose (mmol/L) 90 min | 8.7 | 8.7 | 8.7 |
| Glucose (mmol/L) 150 min | 12.9 | 12.9 | 12.9 |
| Glucose (mmol/L) 270 min | 18.3 | 18.3 | 18.3 |

Data are presented as means ± SEM. Statistical effects (treatment [saline/Ex-9], group status [Asym-GB/Hypo-GB/control subjects], and their interaction) using two-way repeated-measures ANOVA are provided in the last three right-hand columns. Glucagon and GIP values were measured for 29 (11 Asym-GB, 11 Hypo-GB, and 7 control subjects) and 33 (12 Asym-GB, 12 Hypo-GB, and 9 control subjects) subjects, respectively. GINF, glucose infusion rate.
between the two surgical groups. Based on these findings, it appears that GB surgery causes increased GLP-1 secretion and action, effects that are likely to contribute to the changes in glucose metabolism seen in patients after this procedure. However, the disproportionate effect of GLP-1 on insulin or glucagon secretion does not seem to be the sole factor for development of post-GB hypoglycemia syndrome.

The primary goal of this study was to elucidate the role of GLP-1 action in postprandial islet hormone secretion after gastric bypass surgery. To that end individuals with GB were compared with those who did not have prior GI surgeries as well as to the subgroup of subjects suffering from hypoglycemia after GB representing an extreme phenotype of postprandial hyperinsulinemia after GB. Based on the glycemic response to meal ingestion, the two GB groups differed in their propensity to develop blood glucose levels <2.8 mmol/L, a range typically considered pathologic (18). While there was some overlap in glycemia after the MTT, the Asym-GB and Hypo-GB groups segregated regarding their symptomatic response to hypoglycemia as well as the average of their nadir glucose levels during MTT, indicating that each group represents a distinct metabolic phenotype after GB.

Insulin secretion in response to IV glucose stimulation was comparable among the three groups, as was an estimate of insulin sensitivity. These findings suggest that the relatively higher postprandial insulin responses seen in patients after GB (8,9,12,23) are not a response to insulin resistance or the result of general hypersensitivity of β-cells to glucose. Rather, the striking difference in ISR among GB compared with control subjects seems to be limited to the postprandial period and in this study was not statistically distinguishable between subjects with and without the hypoglycemia.

Previous studies have established that the incretin effect, β-cell secretion activated by eating, is increased in GB patients with type 2 diabetes (6,9). Moreover, GLP-1 has been proposed as the mediator of postprandial hyperinsulinemia after GB (8,12,23) and by extension postprandial hypoglycemia (16). Consistent with the greater relative increase of ISR after meal ingestion in GB groups, there was a greater contribution of GLP-1 to postprandial insulin secretion compared with the subjects that did not have surgery. In this study, GLP-1 concentrations were considerably higher in the GB subjects than control subjects, and were higher in the Hypo-GB patients than the Asym-GB patients, as reported previously (8,12,16,23). However, despite having higher plasma GLP-1, the Hypo-GB subjects had estimated GLP-1 effects that were not significantly different from those of the Asym-GB group. There was a weak trend for the Hypo-GB cohort to have a larger relative

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**FIG. 2.** Blood glucose levels and insulin response during oral-IV hyperglycemic clamp with Ex-9 (dashed line, open symbols) or saline infusion (solid line, closed symbols) in Asym-GB (**left**), Hypo-GB (**middle**), and nonsurgical control subjects (**right**). Blood glucose (**A**), insulin (**B**), and insulin secretion rates (**C**) are shown. Data are presented as means ± SEM.
reduction of insulin secretion with Ex-9 than the Asym-GB subjects, and the small sample in this study limits statistical power. However, given the variance in our sample it would require ~80 subjects in each of the Asym-GB and Hypo-GB groups for the apparent difference in GLP-1 mediated insulin secretion to reach statistical significance. Therefore, it seems safe to conclude that recurrent symptomatic hypoglycemia in GB subjects is not primarily due to a disproportionate incretin effect of GLP-1 to drive insulin secretion.

Three other aspects of insulin secretion in this study bear mention. First, the pattern of insulin secretion in the GB subjects after meals differed substantially from the nonsurgical control subjects, with a rapid and accentuated peak in the 1st h and a significant decline thereafter despite persistent clamped hyperglycemia. The early rise in ISR is consistent with increased GLP-1 and GIP stimulation, and in fact the profile of insulin secretion in the GB groups mimics that of the incretins (Figs. 2 and 3). Second, the GLP-1 effect was consistent throughout the 3-h period after meal ingestion even though the highest plasma GLP-1 levels were in the 1st h after meal ingestion. This finding suggests persistent effects of GLP-1r activation even after plasma levels have waned. Finally, as noted previously (19,24), GLP-1r blockade reduced the β-cell response to IV glucose-induced hyperglycemia during the 60–90 min period when there is no nutrient stimulation of GLP-1 secretion. For these latter two findings, the dissociation of plasma GLP-1 values and the GLP-1 effect suggests that activation of the GLP-1r is not entirely explained by changes in plasma concentrations of the peptide.

In our GB subjects, α-cell function also differed dramatically compared with nonoperated control subjects. Previous studies have reported that glucagon secretion after GB is elevated after meal ingestion (9,16,25) and is not altered among subjects with recurrent hypoglycemia (16). In our subjects, glucagon was suppressed by IV glucose in GB and control subjects alike, indicating that surgery did not alter the inhibitory effects of glucose or insulin on α-cells (26,27). However, glucagon levels rose significantly after meal ingestion in both GB groups compared with non-surgical control subjects despite ongoing hyperglycemia. The lack of suppressibility of glucagon secretion after a meal could be attributed to enhanced neural stimulation (28,29) or increased α-cell stimuli such as GIP (30) or GLP-2 (31). Alternatively it is possible that L cells produce and release glucagon in individuals with GB. Because Ex-9 significantly increased postprandial glucagon levels, it appears that the known actions of GLP-1 on α-cells was retained in the GB subjects despite their abnormal prandial glucagon levels.
responses. Similar to changes in β-cell function, the alteration in α-cell regulation in subjects with GB also occurred exclusively in the postprandial state, consistent with enhanced nutrient or neural stimulation of the islets.

In summary, we have demonstrated that in individuals with GB there is an enhanced effect of GLP-1 to promote postprandial insulin secretion. However, increased GLP-1 action while glucose levels are maintained elevated is comparable in GB subjects with and without recurrent hypoglycemia. The distinct patterns of insulin and glucagon secretion after meals in our surgical cohort suggest that regulatory influences on islet function are dramatically altered by GB. The etiology of the post-GB hyperinsulinemic hypoglycemic syndrome is likely to be complex and not the result of enhanced GLP-1–stimulated insulin secretion alone.

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M.S. designed the study, recruited subjects, supervised the studies, collected and analyzed the data, and wrote the manuscript. R.L.P. calculated insulin secretion rates and reviewed and edited the manuscript. D.A.D. designed the study, supervised the assays, and reviewed and edited the manuscript.

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