Glucagon-like peptide 1 (GLP-1) is a peptide hormone that is released from the gut in response to nutrient ingestion and that has a range of metabolic effects, including enhancing insulin secretion and decreasing food intake. Postprandial GLP-1 secretion is greatly enhanced in rats and humans after some bariatric procedures, including vertical sleeve gastrectomy (VSG), and has been widely hypothesized to contribute to reduced intake, weight loss, and alterations in eating behavior. This hypothesis has been tested using two separate models of GLP-1 receptor deficiency. We found that VSG-operated GLP-1 receptor-deficient mice responded similarly to wild-type controls in terms of body weight and body fat loss, improved glucose tolerance, food intake reduction, and altered food selection. These data demonstrate that GLP-1 receptor activity is not necessary for the metabolic improvements induced by VSG surgery. *Diabetes* 62:2380–2385, 2013

**Glucagon-like peptide 1 (GLP-1)** is a hormone that is released from L-cells of the small intestine in response to nutrient ingestion. GLP-1 is most well-known for its effect as an incretin, stimulating insulin secretion from pancreatic β cells, but it also has a wide range of other effects, including the reduction of food intake and improvement of various aspects of glucose tolerance beyond its ability to augment insulin secretion. Long-acting GLP-1 receptor agonists are used as therapies for type 2 diabetes and convey the additional benefit of weight loss in many patients (1).

Bariatric surgery is the most effective weight loss treatment, surpassing drug therapies and lifestyle interventions (2). Vertical sleeve gastrectomy (VSG) is a bariatric procedure that involves the removal of ~80% of the stomach along the greater curvature, creating a gastric “sleeve” in continuity with the esophagus and pylorus. VSG induces loss of body weight and fat mass and improves glucose tolerance in humans and in rodent models (3–8). For example, a recent randomized controlled trial that compared VSG, Roux-en-Y gastric bypass (RYGB), and medical management (9) found that VSG and RYGB produced similar percentage of patients whose diabetes had gone into remission after 1 year and both procedures were significantly superior to medical management. Although RYGB classically has been considered the gold standard for bariatric procedures, VSG is rapidly gaining in popularity and its utilization is increasing. Consequently, it is an important research and clinical goal to understand the underlying mechanisms for these potent effects of VSG.

Multiple reports show that weight-reduction bariatric procedures such as VSG and RYGB result in dramatically enhanced meal-stimulated GLP-1 secretion (6,10,11), leading to the hypothesis that GLP-1 action underlies many of the metabolic improvements caused by these surgeries. GLP-1 has one known receptor (GLP-1r), and mice that lack this receptor (GLP-1r knockout [KO]) are insensitive to the effects of exogenously administered GLP-1. These mice have impaired glucose tolerance (12,13). We tested the hypothesis that GLP-1 action is necessary for the effects of VSG by performing VSG surgery in two separate models of whole-body GLP-1r deficiency and by examining their metabolic and behavioral outcomes.

**RESEARCH DESIGN AND METHODS**

All procedures for animal use were approved by the University of Cincinnati Institutional Animal Care and Use Committee. Mice were maintained on a 12-h/12-h light–dark cycle with light onset at 1:00 A.M.

**Experiment 1.** A cohort of C57Bl6 mice used to determine postprandial GLP-1 levels after VSG were bred in-house from breeders purchased from Jackson Laboratories and maintained on a high-fat butter-based diet (D12492 [60% fat, 5.24 kcal/g]; Research Diets, New Brunswick, NJ). Weight-matched mice received either VSG (n = 5) or sham (n = 7) surgery. At 12 weeks postoperatively, mice were fasted for 4 h in the middle of the light cycle before receiving a gavage of 200 µL of Ensure Plus liquid diet; 15 min later, mice were placed briefly in a CO2 chamber and were then killed by decapitation. Trunk blood was collected in tubes treated with a protease inhibitor cocktail of EDTA, Aprotinin, and heparin, and 25 µL plasma was used for measurement of GLP-1 (Meso Scale Discovery, Gaithersburg, MD).

**Experiment 2.** GLP-1r wild-type (WT) and KO mice (n = 13) were generated from homozygous breeding pairs, which were F1 offspring from GLP-1r heterozygote breeders. KO (n = 31) and WT (n = 24) mice were placed on a high-fat butter-based diet (D03082706 [40% fat, 4.54 kcal/g]; Research Diets, New Brunswick, NJ) for 5 weeks starting at age 4–8 weeks, at which point each was subdivided into 2 body weight and fat mass–matched groups (VSG and sham) before gastric surgery. Postoperative deaths, mainly within the first week, yielded final group numbers of 8 WT sham, 11 WT VSG, 12 KO sham, and 16 KO VSG. Common reasons for postoperative death included bleeding, infection, and gastric obstruction. The mice were maintained on high-fat diet after surgery except during the immediate postoperative period and during diet choice testing, as noted. Body weight and food intake were measured by weighing the mice and their food hoppers daily or weekly. A continuous monitoring system (TSE Systems, Chesterfield, MO) was used to obtain detailed food intake data from days 28–31.

**Surgery.** VSG surgery was performed using isofluorane anesthesia. The lateral 80% of the stomach was excised, leaving a tubular gastric remnant in continuity with the esophagus superiorly and the pylorus and duodenum inferiorly. The
sham procedure involved analogous isolation of the stomach followed by manually applying pressure with blunt forceps along a vertical line between the esophageal sphincter and the pylorus. Mice consumed liquid diet (Osmolite OneCal) for the first 4 postoperative days and were reintroduced to solid food (high-fat diet) on day 5.

**Macronutrient selection.** Food choice was assayed from postoperative days 11–17 using a macronutrient selection paradigm in which three pure macronutrient diets (TD.02521 [carbohydrate], TD.02532 [fat], and TD.02523 [protein]; Harlan Teklad) were presented simultaneously in separate containers. The first 2 days were acclimation, and data from the final 4 days are presented. Because of diet splitting by some mice, analysis was limited to six WT sham, seven WT VSG, nine KO sham, and 12 KO VSG mice.

**Body composition.** Magnetic resonance imaging was performed on day 21 to determine body composition using a whole-body composition analyzer (EchoMedical Systems, Houston, TX).

**Mixed-meal tolerance test.** A mixed-meal tolerance test was performed on postoperative day 18. Mice were fasted for 4 h beginning 5 h after the initiation of the light phase of the light–dark cycle. After a baseline blood sample was taken (0 min), 200 μL Ensure Plus liquid diet (1.41 kcal/g, 20% fat; Abbott Nutrition, Columbus, OH) was delivered by intragastric gavage. Blood glucose was measured at 0, 15, 30, 45, 60, and 120 min after nutrient administration on duplicate samples using Accu-chek glucometers and test strips (Roche, Indianapolis, IN). All blood samples were obtained from the tip of the tail vein of freely moving mice. An additional 50 μL blood was collected in heparinized tubes at times 0 min and 15 min to measure plasma insulin concentration. Blood was cold-centrifuged and plasma was stored at −80°C until insulin was assayed by ELISA (CrystalChem, Downers Grove, IL).

**Anorexic response to exendin-4.** On day 41, all mice were fasted for 4 h before the onset of the dark phase of the light–dark cycle (t = 0 h). Exendin-4 (400 μg/kg, intraperitoneal) was injected at 1 h, and food was returned at 0 h. Food intake was measured at 2, 4, and 24 h. On the previous day, a procedurally identical experiment was conducted using an injection of intraperitoneal saline. Data shown are the difference in food intake per mouse between exendin-4 treatment and saline treatment.

**Experiment 3.** We generated a separate mouse model of GLP-1r deficiency using a Cre-lox system, as described (Supplementary Fig. 1). Briefly, we generated mice with loxp sites flanking exons 6 and 7 of the GLP-1r gene and crossed with mice that express Cre recombinase driven by the cytomegalovirus minimal (CMV) promoter. In CMV-Cre mice, deletion of loxp-flanked genes occurs in all tissues, including germ cells (14). Thus, mice that are homozygous for GLP-1r flox and hemizygous for CMV-Cre (GLP-1r flox/CMV-Cre) lack the GLP-1r in all tissues. Littermates that were hemizygous for CMV-Cre and WT for the GLP-1r (CMV-Cre) were used as controls. Gene expressions of GLP-1r exons 6 and 7 were determined by quantitative PCR and normalized to expression of L32. Experimental procedures, including surgery, mixed-meal tolerance test, and the anorexic response to exendin-4, were determined as described for experiment 2. Group sizes were as follows: 7 in CMV-Cre sham group, 7 in CMV-Cre VSG group, 11 in GLP-1r flox/CMV sham group, and 17 in GLP-1r flox/CMV VSG group. The mixed-meal tolerance test was performed 5 weeks after surgery, and the food intake response to exendin-4 was conducted 10 weeks after surgery.

**Statistics.** All data are presented as mean ± SEM. Data were analyzed using the appropriate test, two-way ANOVA, or three-way ANOVA. When appropriate, Tukey post hoc comparisons were used to determine pair-wise differences between groups. $P < 0.05$ was considered significant for each of these analyses. Data were analyzed using GraphPad (Prism, San Diego, CA) and SigmaStat (Systat Software, Chicago, IL).

## RESULTS

**Experiment 1: Postprandial GLP-1 in VSG-operated mice.** Fifteen minutes after a mixed-meal gavage, VSG-operated mice exhibited much higher total plasma GLP-1 levels than sham-operated controls (Fig. 1A; $t$ test, $P = 0.0002$), confirming that mice show a similar GLP-1 response to VSG surgery compared with humans and rats.

**Experiment 2: VSG surgery in GLP-1r KO mice.** KO mice weighted significantly less than WT mice at the time of surgery (two-way ANOVA, main effect of genotype, $P = 0.0001$), which occurred after 5 weeks of exposure to high-fat diet. VSG induced weight loss in both WT and KO mice (Fig. 1B; three-way ANOVA, main effect of genotype), an effect that was sustained for the duration of the experiment. When expressed as a percent change in body weight (Fig. 1C), WT sham and KO sham groups do not significantly differ, nor do WT VSG and KO VSG groups.

Body composition analysis revealed that VSG caused loss of fat mass in both WT and KO animals, with KO mice having less fat mass than the corresponding WT group (Fig. 1D; two-way ANOVA, main effect of genotype, $P = 0.001$; two-way ANOVA, surgery, $P < 0.001$). Lean mass was unchanged by the surgery, but lower in KO than in WT mice (Fig. 1E; main effect of genotype, $P < 0.001$). Percent change of fat mass was similar between WT and KO mice (main effect of surgery, $P = 0.001$), and percent change of lean mass was similar among all groups (Supplementary Fig. 2).

To verify that the GLP-1r KO mice had functional loss of GLP-1 receptors (in addition to genotyping by PCR), we challenged the mice with an intraperitoneal injection of the GLP-1r agonist exendin-4, which potently decreases food intake by acting on the GLP-1r. WT mice had the predicted hypoglycemic response, decreasing their 24-h food intake relative to a saline injection, whereas GLP-1r KO mice were unresponsive to the treatment (Fig. 1F; $t$ test, $P < 0.0001$).

Blood glucose was measured after oral administration of Ensure Plus liquid diet to assess glucose excursions in response to a mixed meal (Fig. 2A). KO sham mice had significantly elevated glucose excursions compared with WT sham ($P < 0.001$ at 45 min and 60 min), and VSG-operated mice of both genotypes had lower glucose levels than the sham-operated groups and did not differ from each other (WT sham vs. WT VSG $P = 0.01$ at 30 min; KO sham vs. KO VSG $P = 0.05$ at 15–120 min). Fasting glucose (baseline for the mixed-meal tolerance test) was significantly lower in VSG-operated mice as compared with sham-operated mice of both genotypes (two-way ANOVA of 0 time point, main effect of surgery, $P < 0.0001$). Baseline fasting insulin levels revealed an effect of both surgery ($P = 0.0068$) and genotype ($P = 0.0006$), with WT and sham animals having higher insulin levels than KO and VSG counterparts (Fig. 2B). At 15 min, WT and KO VSG mice increased insulin levels to a similar extent compared with sham controls (Fig. 2C; main effect of surgery, $P = 0.0012$).

In the first 3 postoperative days, VSG-operated mice exhibited lower food intake than sham-operated mice of both genotypes (Fig. 2D; two-way ANOVA, main effect of surgery, $P = 0.0001$) and gradually increased their energy intake through the second postoperative week (Supplementary Fig. 3). Three-day food intake was measured from days 28–31 (Fig. 2D), at which time KO mice ate less than WT mice (Fig. 3D; two-way ANOVA, main effect of genotype, $P = 0.008$), likely because of the decreased body mass of the KO animals. A macronutrient selection paradigm, in which mice were allowed to self-select their diet from pure macronutrient sources, was used to assess food choice during the second postoperative week (Fig. 2E). VSG altered food choice in WT mice by decreasing fat intake ($P < 0.01$), increasing carbohydrate intake ($P < 0.01$), and increasing protein intake ($P < 0.01$), an effect that we have recently demonstrated in rats (15). VSG had a similar effect in KO mice ($P < 0.01$; carbohydrate, $P < 0.01$) but did not alter protein intake (three-way ANOVA surgery × diet, $P < 0.001$; genotype × diet, $P = 0.008$).

**Experiment 3: VSG surgery in a new model of global GLP-1r deficiency.** GLP-1r flox/CMV mice and CMV-Cre littermate controls were investigated for expression of the loxp-floxed segment of the GLP-1r gene (exons 6 and 7) and normalized to expression of L32. Compared with
CMV-Cre controls, GLP-1r flACMV mice had negligible GLP-1r expression in pancreas, lung, and hypothalamus (Fig. 3A; t test, P < 0.001 in all cases). A separate cohort of GLP-1r flACMV mice and CMV-Cre littermate controls were challenged with an intraperitoneal injection of exendin-4 to determine whether this model of global GLP-1r deficiency was truly insensitive to the hypophagic effect of a potent GLP-1r antagonist. Similar to the results obtained in experiment 2, the control mice significantly decreased their food intake compared with their response to a saline injection, whereas the GLP-1r flACMV mice showed no hypophagic response (Fig. 3B; t test, P < 0.0001). VSG induced weight loss compared with sham-operated mice in both CMV-Cre and GLP-1r flACMV mice (Fig. 3C; three-way ANOVA, main effect of genotype, P < 0.001; three-way ANOVA, surgery, P < 0.001), but there was no statistical interaction of genotype and surgery (P = 0.326), indicating that VSG is equally effective in both genotypes. The results of the mixed-meal tolerance test (Fig. 3D) are similar to the results obtained using the established GLP-1r KO mice (Fig. 2A). VSG-operated mice of both genotypes exhibited a significant improvement in blood glucose excursions, and sham GLP-1r flACMV mice tended to be more glucose-intolerant than the sham controls (three-way ANOVA, main effect of surgery, P < 0.001; three ANOVA, genotype, P = 0.015; three-way ANOVA, surgery × genotype interaction, P = 0.679).

**DISCUSSION**

Here, we show that mice lacking GLP-1r respond just as well as WT mice after VSG surgery in terms of reduced body weight and body fat improvements in glucose homeostasis and altered food choice. Importantly, VSG overcomes the presurgical glucose intolerance of GLP-1r–deficient mice, decreasing the glucose excursions to WT VSG levels. Given that GLP-1 has been widely hypothesized to be responsible for VSG-induced improvements in glucose tolerance, it is especially surprising that mice that lack GLP-1 action show a paradoxically greater magnitude of improvement than WT animals. Our data demonstrate that large-magnitude improvements in glucose tolerance occur even in the absence of GLP-1r signaling; therefore, GLP-1r activity is not necessary to manifest the beneficial effects of VSG surgery.

We have to admit that these data surprised us. The outcome stands in stark contrast to our original hypothesis and do not directly support the conclusions of several other studies that implicate GLP-1 in the outcomes of RYGB surgery. For example, one 2007 study showed that meal-induced GLP-1 (and peptide YY [PYY]) excursions are higher in RYGB patients with superior weight loss compared with those who did not achieve sufficient weight loss (16). Moreover, the same study showed that somatostatin, which inhibits the release of those hormones from the intestine, increased food intake in RYGB but not in

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**FIG. 1.** The effect of VSG on body weight and body fat in GLP-1r KO mice. VSG-operated mice (n = 5 VSG; n = 7 sham) show significantly elevated plasma GLP-1 15 min after gavage of a mixed meal (A). After 5 weeks of high-fat feeding, GLP-1r WT and KO mice underwent VSG or sham surgery (n = 8 WT sham; n = 11 WT VSG; n = 12 KO sham; and n = 16 KO VSG). Body weight (B) and weight change from the time of surgery (C) were monitored, and body composition (D and E) was assessed on postoperative day 21. The food intake response to the GLP-1r agonist exendin-4 (F) is shown as the difference between 24-h food intake after exendin-4 and saline treatment. Data are represented as mean ± SEM. *P < 0.05; ***P < 0.001.
adjustable gastric band patients, in whom GLP-1 and PYY release are not increased. The implication is that more robust GLP-1 and PYY excursions directly reduce food intake and lead to body weight loss.

Three additional reports, including one from our own group, have used the GLP-1r antagonist exendin-9 to demonstrate that surgery-induced improvements in glucose homeostasis are attenuated when GLP-1 action is blocked. Kindel et al. (17) demonstrated that Goto-Kakizaki rats that undergo duodenal-jejunal exclusion exhibit a small improvement in glucose tolerance, but that the effect is abolished after a subcutaneous injection of exendin-9. Similarly, we showed that exendin-9 undermined the improvements in glucose tolerance of RYGB and VSG-operated diet-induced obese rats (10). Finally, a human study of weight-stable RYGB patients demonstrated that meal-stimulated insulin secretion, which is higher in RYGB compared with control subjects, was suppressed to a greater degree by exendin-9 in RYGB patients (18). All of the studies suggest that acute pharmacological manipulation of GLP-1r signaling is sufficient to reduce the benefit of VSG on the response to a glucose load.

Studying a human-specific procedure such as bariatric surgery in an animal model has benefits as well as caveats. In mouse experiments such as these, the inclusion of appropriate control groups, such as sham surgery, as well as the ability to control for many factors (diet, exercise, environment) are clear advantages. However, rodents continue to grow and gain body mass throughout their lifetime. This is different from humans. As such, mice that receive bariatric surgery will likely eventually meet and surpass their presurgical body weight. It is important to note, though, that we and others have found that VSG- or RYGB-operated rodents maintain lower body weight compared with sham-operated controls throughout their lifetime (10,19). Across a wide range of physiological phenomena, effects in rodents closely parallel observations in human bariatric patients, including the dramatic increases in GLP-1 secretion (6,10).

There are a number of advantages to the use of genetic KO models to study the role of GLP-1 in bariatric surgery as compared with these examples of a pharmacological approach. Exogenous administration of the GLP-1r antagonist exendin-9 has several uncertainties, including the degree of GLP-1r blockade, potential nonspecific effects of the antagonist, partial agonist activity, and the temporal period for which the receptor blockade is achieved. The genetic approaches used here provide unequivocal long-term disruption of the GLP-1r in all tissues and consequently provide experimental benefits when trying to examine the effect of a chronic treatment such as a bariatric procedure like VSG. These advantages need to be weighed against the possibility that whole-body genetic KO models of any kind might result in developmental compensation. As such, it is possible that this approach underestimates the role of GLP-1 to contribute to the effects of VSG. At least two cases of compensation in GLP-1r KO mice have been reported, indicating enhanced

FIG. 2. Metabolic effects of VSG in GLP-1r KO mice. GLP-1r WT and KO mice that received VSG or sham surgery underwent a mixed-meal tolerance test on postoperative day 18 (n = 8 WT sham; n = 11 WT VSG; n = 12 KO sham; and n = 16 KO VSG). Blood glucose (A) was measured after gavage of a standard liquid diet, and plasma insulin was determined at baseline (B) and 15 min (C). Food intake (D) was significantly lower in VSG-operated mice of both genotypes from days 0–3, but by days 28–31 there was no effect of surgery and KO mice consumed less than WT controls. Food choice was assessed by macronutrient selection (n = 6 WT sham; n = 7 WT VSG; n = 9 KO sham; and n = 12 KO VSG), showing that VSG mice of both genotypes decrease fat intake and increase carbohydrate intake (E). Data are represented as mean ± SEM. **P < 0.01; ***P < 0.001.
action of GLP-2 (20) and glucose-dependent insulinotropic peptide (21) compared with WT controls. Thus, one hypothesis is that the potential increases in gastric inhibitory polypeptide or GLP-2 could compensate for the lack of GLP-1r signaling. However, GIP has been shown to promote fat accumulation (22), which does not fit with the phenotype of the GLP-1r KO mice before or after VSG surgery. Furthermore, even if this were true, it is difficult to reconcile why the GLP-1r KO mice do not have normal glucose tolerance until after VSG. Regarding the role of GLP-2, although it may decrease food intake, it has no known effects on glucose tolerance (22). Thus, although developmental compensation is a potential explanation for results such as these, there is not a straightforward hypothesis about the nature of developmental compensation that would account for the present data.

Here, the GLP-1r KO mice from experiment 2 had lower body weight and fat mass than the WT controls both before and after surgery. Although we can offer no explanation why lack of GLP-1r signaling would cause this phenotype, our data fit with previous reports (12,23) that showed that GLP-1r KO mice maintained on chow diet do not have normal glucose tolerance until after VSG. Regarding the role of GLP-2, although it may decrease food intake, it has no known effects on glucose tolerance (22). Thus, although developmental compensation is a potential explanation for results such as these, there is not a straightforward hypothesis about the nature of developmental compensation that would account for the present data.

In conclusion, the studies described here, like all lack-of-function experiments, test whether a factor (in this case, the GLP-1r) is necessary for the effect of interest. They do not address whether that same factor is sufficient for the effect or whether it may play some other kind of role. As such, we cannot rule out that GLP-1 may contribute to the effects of VSG, including weight loss, glucose tolerance, and altered food choice. However, we can say with certainty that it is not strictly necessary. Thus, because the GLP-1r is not required to manifest the dramatic effects of VSG, other factors or systems must contribute to the beneficial effects of VSG.

Using two independent models of genetic disruption of the GLP-1r, our data clearly demonstrate that GLP-1r activity is not necessary for VSG to exert its potent effects on a range of metabolic and behavioral end points. Given the similarity of the enhanced postprandial GLP-1 responses in both VSG and RYGB (4,6,10), as well as their similar effects on insulin secretion, hepatic glucose production, and food choice (4,10,15), the primacy of GLP-1 as the primary mediator of the pleiotropic metabolic benefits of bariatric surgery requires reconsideration.

FIG. 3. VSG in a new model of GLP-1r deficiency. Expressions of GLP-1r exons 6 and 7 were analyzed in pancreas, lung, and hypothalamus of CMV-Cre (control n = 6) and GLP-1r ΔExons 6 and 7 (KO n = 9) mice (A). Mice were tested for their food intake response to the GLP-1r agonist exendin-4 (B). Data are shown as the difference between 24-h food intake after exendin-4 and saline treatment. Body weight change (C) was monitored after VSG or sham surgery (control sham n = 7; control VSG n = 7; KO sham n = 11; KO VSG n = 17), and a mixed-meal tolerance test (D) was conducted 5 weeks postoperatively. Data are represented as mean ± SEM. ***P < 0.001.

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H.E.W.-P. led the project in study concept/design, data acquisition, analysis, and manuscript writing. A.P.C. and K.K.R. assisted with data acquisition and interpretation. B.L. generated, validated, and phenotyped mouse models. D.A.S. assisted with interpretation of data and critical manuscript revision. D.S. generated, validated, and phenotyped mouse models. D.J.D. and D.P.-T. contributed material support and critically revised the manuscript. R.J.S. obtained funding and provided study supervision. R.J.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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