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Reprogramming of defended body weight after Roux-en-Y gastric bypass surgery in diet-induced obese mice

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Abstract

Objective—Roux-en-Y gastric bypass surgery (RYGB) results in sustained lowering of body weight in most patients, but the mechanisms involved are poorly understood. The aim of this study was to obtain support for the notion that reprogramming of defended body weight, rather than passive restriction of energy intake, is a fundamental mechanism of RYGB.

Methods—Male C57BL6J mice reaching different degrees of obesity on a high-fat diet either with ad libitum access or with caloric restriction (weight-reduced) were subjected to RYGB.

Results—RYGB-induced weight loss and fat mass loss was proportional to pre-surgical levels, with moderately obese mice losing less body weight and fat compared with very obese mice. Remarkably, mice that were weight-reduced to the level of chow controls before surgery, immediately gained weight after surgery, exclusively accounted for by lean mass gain.

Conclusions—The results provide additional evidence for re-programming of a new defended body weight as an important principle by which RYGB lastingly suppresses body weight. RYGB appears to selectively abolish defense of a higher fat mass level, while remaining sensitive to the defense of lean mass. The molecular and physiological mechanisms underlying this re-programming remain to be elucidated.

Keywords

Bariatric surgery; obesity; energy expenditure; food intake; calorie restriction; body composition

Introduction

Bariatric surgeries are increasingly used to reduce body weight and improve metabolic health, but the mechanisms leading to these beneficial effects are not well understood. Specifically, it is not clear whether reduced food intake and body weight are the result of restriction and malabsorption or a change in actively defended body weight (our working definition of the behavioral implications of the term “body weight set point”). If the former were true, bariatric surgery patients would show the classical signs of starvation such as

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being constantly hungry, reducing basal metabolic rate, and suppression of satiation mechanisms including gastrointestinal hormone secretion. These typical starvation responses would not be expected if bariatric surgeries were to lower the defended body weight level.

Clinical studies in Roux-en-Y gastric bypass patients provide at least some support for both explanations. Most patients are less hungry and lose the desire to eat and the preoccupation with food and food cues (1–4), as also reflected by the large and sustained decrease of food intake generally observed (5–7). However, the elevated craving for fatty foods in obese patients does not seem to be affected by RYGB, and a significant number of patients do fight feelings of hunger and food cravings (8), likely resulting in resistance to weight loss or significant weight regain (9). Also, most studies in humans find that basal metabolic rate is decreased rather than increased, although the decrease appears to be less than expected from the weight loss (see (10, 11) for recent reviews). Support against a restriction/starvation mechanism comes from the widely observed increases in circulating levels of gastrointestinal hormones such as GLP-1 and PYY[3–36] that occur in both humans and rodents after gastric bypass surgery but not after caloric restriction [e.g. (12, 13)].

Several recent rodent studies provide additional support against the restriction/starvation and for the defense of a lower body weight explanation. Rats with vertical sleeve gastrectomy that are additionally food restricted will increase food intake and regain body weight to pre-restriction levels but not beyond (14). Rats with RYGB that have been rendered hyperphagic and obese by chronically blocking brain MC4-receptor signaling return to pre-treatment body weight, clearly demonstrating that food intake is not restricted and that a lower level of body weight appears to be defended (15). In addition, and in contrast to human studies, most rodent studies report increased basal metabolic rate after RYGB (16–19). Also in contrast to human studies, rat studies have shown that food intake returns to pre-surgical levels relatively quickly after surgery, indicating that increased energy expenditure seems to be an important mechanism for defending the lower body weight level.

To further strengthen the interpretation that RYGB is not indiscriminately restrictive, but rather establishes a new, lower body weight that is physiologically defended, we examined the effects of RYGB on food intake, body weight, body composition, and energy expenditure in mice with different degrees of obesity. In particular, we included mice whose obese body weight was reduced by caloric restriction below their defended weight prior to RYGB to test whether food intake and body weight would be paradoxically increased, rather than decreased, after surgery.

Materials and Methods

Animals and Diets

Male C57BL6J mice (Jackson Laboratories, Bar Harbor ME) were group housed (3–4 per cage) in shoebox cages with corn cobb bedding in a temperature (22 ± 1 °C) controlled room with a 12 h light/dark cycle (lights on at 0600h, lights off at 1800h). At the age of about 6 weeks, they were given a two-choice diet consisting of normal laboratory chow (Kcal%: Carb, 58; Fat, 13.5; Prot, 28.5, #5001, Purina LabDiet, Richmond IN) and high-fat diet (Kcal%: Carb, 25; Fat, 60, Prot 15, D12331, Research Diets, New Brunswick, NJ) throughout

the study. After 12–14 weeks on the diet, they were stratified on the basis of body weight and fat mass and assigned to the different experimental groups. Additional age-matched mice were given regular chow throughout the study. All protocols were approved by the Institutional Animal Care and Use Committee at the Pennington Biomedical Research Center in accordance with guidelines established by the National Institutes of Health.

Gastric bypass surgery

The surgical procedure has been described in detail earlier (18). Briefly, it consisted of transecting the jejunum below the ligament of Treitz, and forming a 5–6 cm long Roux- and a 7–8 cm long biliopancreatic limb by anastomosing the distal cut end of the jejunum to a small gastric pouch of less than 5% of stomach volume and the proximal cut end to the mid-jejunum in overnight food-deprived mice. Sham surgery consisted of performing laparotomy and mobilization of the small intestine. No special diet was provided and all animals ate solid high-fat diet and regular chow starting on the day after surgery. There were no complications and no mortality.

Calorie restriction-induced weight loss for weight-matching

To match the body weight of RYGB animals in a non-surgical group, access to the high/low-fat choice diet was restricted. Premeasured amounts (50–70% of normal intake) of both diets were given during the light period, at the time of weighing.

Measurements of body composition, food intake and food choice

Body composition was measured with whole body NMR (Minispec LF50, Bruker, Woodland, TX) before and every 2 weeks after surgery. The NMR scanner provides measurements of fat mass, fat free mass (or here labeled as lean mass), and fluid mass. Calculations of percent fat mass or lean mass were based on the sums of these three compartments, not actually measured body weight (which is typically slightly higher). The adiposity index was obtained from dividing fat mass by lean mass. Excess body weight was defined as amount of body weight above the average body weight of chow-fed, age-matched mice.

Food intake for both diets was measured in grams by subtracting any amount left in the cage plus spillage recovered from below the grid floor, from a pre-weighed amount given to each mouse between 9 am – 12 noon. Energy intake was obtained by multiplying grams eaten by the caloric density of 5.2 Kcal/g for high-fat diet and 3.02 kcal/g for chow diet. Energy intake from both diets was added for total daily energy intake. Preference for regular chow was calculated by the formula: energy from chow/energy from chow + energy from high-fat diet $\times$ 100.

Statistical analysis

One-way ANOVA was used to analyze body weight loss, fat mass loss, lean mass loss, and adiposity index. Two-way repeated measures ANOVA was used to analyze body weights as well as food intake and changes in body composition in the calorie restricted groups. All ANOVAs included Bonferroni-corrected multiple comparison follow-ups. All data was expressed as mean $\pm$ SEM. Linear regression was performed to determine the value of pre-

surgical body weight as a predictor for changes in body weight, fat mass, lean mass, and adiposity index following surgery. Significance for all analyses was accepted at the $p < 0.05$ level.

Results

Our own surgical technique (18, 20, 21) has further matured so that there was no mortality or complications in the 28 mice with RYGB surgery in the present study. RYGB mice were able to ingest solid food as early as one day after surgery and food intake recovered to near pre-surgical levels within about 10 days. As a result, surgery-induced body weight loss was gradual over the first 1–3 weeks after surgery. This is in contrast to the much larger early weight loss after one week of surgery reported in other mouse models of RYGB in which animals are typically fed liquid diets for a period of 7–10 days after surgery and mortality can reach as much as 50% (19, 22–25)

We took advantage of the fact that, even in these inbred mice, exposure to the high-fat diet increased body weight and fat mass variably, with some animals getting very obese and others being almost resistant. We thus analyzed the effects of RYGB in mice with high, medium, and low initial body weight/fat mass and further examined starting body weight as a predictor of total body weight loss and fat mass loss. Because the focus in this study was on changes in body weight and composition after RYGB, and because we have previously shown that sham-surgery produces only transient body weight loss, data for sham surgeries carried out in parallel are reported in the Supplemental data (Fig. S1) and are only mentioned in the text when deemed necessary.

RYGB-induced weight loss is proportional to initial body weight and fat mass

As shown in Fig. 1, the more body weight gained on the high-fat diet prior to surgery, the more body weight was lost after surgery and the longer it took to lose it. However, this tendency did not completely equalize post-surgical body weight among the three groups, as the most obesity prone mice (high) remained slightly heavier than the least obesity prone mice (low) up to 5 weeks after surgery. Furthermore, all mice on high-fat diet weighed significantly more than age-matched mice on regular chow diet at all time points after surgery, even the least obesity-prone mice.

Changes in body weight and composition at 4 weeks after surgery are shown in Fig. 2. They further document that weight loss in the most obese mice is larger than in the least obese mice, even when expressed in percent of starting body weight (Fig. 2A). The same is true for weight loss at 1, 2 and 3 weeks after surgery, except that the percent weight loss at 1 week was not significantly different between the three groups (not shown). Mice with body weights matching the three groups of high-fat fed obese mice were also subjected to sham surgery. All of these animals continued to gain body weight after only a brief initial loss of about 10 % (Fig. S1).

Body composition was assessed one week before and 4 weeks after surgery. Similar to total body weight loss, fat mass loss in grams was significantly greater for the most obese (high) compared with the least obese (low) mice, with the intermediate obese group (mid) between

(Fig. 2B). However, relative fat mass loss in percent of starting fat mass was not significantly different for the three groups.

Changes in lean mass were very small, but nevertheless showed a pattern similar to fat mass, with the most obese mice losing about 0.5 g (~2%) and the least obese mice gaining about 1 g (~4%) of lean mass (Fig. 2C). The change in adiposity index also reflects the general effect of RYGB - fatter animals show the highest amount of fat loss (Fig. 2D).

Linear regression analysis was used to further characterize initial body weight as predictor of changes in body weight and composition (Fig. 3). The predictive value of pre-surgical body weight across all three groups (low, med, high) was highest for absolute body weight loss (Fig. 3A), but still significant for percent body weight loss (Fig. 3B). Similarly, pre-surgical body weight was a strong predictor of absolute fat mass loss (Fig. 3C), but only a weak predictor for lean mass loss (Fig. 3D). The change in adiposity index was also significantly predicted by the initial body weight. However, initial body weight was not a predictor of percent excess body weight loss, which was based on differences between body weight of the high-fat fed obese and chow-fed, age-matched mice (Fig. 3E). Using pre-surgical fat mass instead of body weight as predictor did not substantially change this pattern and the strength of these correlations (data not shown).

Paradoxical rapid body weight gain and food intake after RYGB

The convergence from the widely different body weights before surgery to the relatively narrow range of ~31–34 g after RYGB of the three groups suggested the presence of a new defended body weight. To test this possibility, we performed RYGB in mice that were weight-reduced before surgery. Just like the other three groups, the mice were first made obese on a high-fat diet, and during 3 weeks were given only a fraction of their normal high-fat intake. These calorie-restricted, weight reduced mice reached a body weight at the time of surgery that was similar to the chow-fed controls (Fig. 4A). Somewhat unexpectedly, these mice did not lose any body weight after RYGB. On the contrary, they significantly gained about 4 g (~15%) of body weight to a level near 30 g, which was almost identical to the body weight of the “low” diet-induced obese mice after RYGB (Fig. 1). Similarly weight-reduced mice that received sham surgery gained weight at a faster rate and rapidly surpassed pre-restriction levels (Fig. 4A).

Remarkably, RYGB mice started eating amounts of food that were only slightly lower than intake of high-fat diet in mice without surgery (Fig. 4B). Only during the first 3 days after surgery, did the sham operated mice consume even more food than the RYGB mice.

Calorie-restriction also resulted in loss of fat mass (Fig. 4C), and lean mass (Fig. 4D), but while fat mass did not further change after RYGB, lean mass rapidly increased to pre-restriction levels, at the same rate as in sham-operated mice (Fig. 4D). Fluid mass was also significantly decreased by calorie restriction and increased with weight regain (Fig. 4G,H). However, while sham mice had regained all of the lost fluid mass by 3 weeks after surgery, RYGB mice showed a much smaller increase. Although lean mass significantly increased in RYGB mice, the small changes in adiposity index (Fig. 4E) and leanness (Fig. 4F) did not reach statistical significance.

Discussion

The present findings suggest that RYGB surgery, rather than being restrictive and reducing food intake and body weight indiscriminately, is sensitive to the prevailing body weight and composition, only reducing food intake and body weight if excess fat is present. Although the study does not attempt to identify the mechanisms involved it sheds light on the roles of both fat mass and lean mass in the control of energy balance regulation. Specifically, when lean mass is reduced by caloric restriction prior to RYGB, food intake and body weight are paradoxically increased immediately after RYGB to rapidly restore lean mass, not fat mass. This rapid restoration of lean mass was not due to over-hydration of fat-free mass in RYGB mice, as fluid mass gain was minimal and smaller than in sham mice.

Thus, RYGB appears to selectively abolish regulation of fat mass while defense mechanisms of lean mass remain intact. Independent roles for fat mass and fat-free mass in the homeostatic regulation of body weight are increasingly recognized (26–29). Analyzing the recovery response to caloric restriction-induced weight loss in humans shows the potential to gain back more fat than lean mass because at the time when fat recovery is complete, fat-free mass recovery is still incomplete and continues to drive hunger (26, 27). We also observed this rapid recovery of fat mass in mice subjected to sham surgery after prior caloric restriction-induced weight loss, but not in mice with RYGB.

Previously reported mouse models of RYGB and VSG were unable to properly investigate these early effects of surgery because special liquid diet was provided for up to 10 days after surgery, resulting in much larger initial body weight suppression, reaching as much as 40% after 1–2 weeks (19, 23, 30). In another model where special diet was only provided for two days, mortality reached 50% (22). In our model, even the very obese mice only lost about 15–20 % of body weight during this initial period. The difference is likely to be found in the invasiveness of the surgical procedure.

Consistent with clinical studies (33, 34), we find that both body weight and fat mass loss at 4 weeks are more or less proportional to initial body weight and fat mass. However, the body weight and fat mass plateau which is reached by about 4 weeks after surgery is not the same for mice with different starting body weight and adiposity, as the most obese mice retain some of the extra fat mass after surgery. This finding can be interpreted in different ways. It could mean that mice more prone to the high-fat diet defend a higher body weight/adiposity level even after RYGB surgery compared to mice less prone (or relatively resistant) to the diet. Conversely, it could indicate that the metabolic impairments have rendered these mice more resistant to the consequences of RYGB.

The present findings provide further behavioral but not molecular evidence for the notion that RYGB surgery is able to produce sustained body weight loss by changing the defended level of body weight. Similar conclusions have been made by others using different approaches, bariatric surgeries and species. We have previously demonstrated defense of an RYGB-induced lower level of body weight in rats with RYGB given brain infusions of the melanocortin receptor (MC3/4R) antagonist SHU9119 (15). After inducing hyperphagia and rapid weight gain above pre-surgical levels, rats promptly returned to pre- SHU9119

infusion body weight. Here we demonstrate that mice with a negative perturbation of body weight return to their preferred higher level even immediately after RYGB. It was also shown earlier that rats with vertical sleeve gastrectomy (VSG) challenged by a chronic food restriction responded with higher food intake and return to pre-restriction, rather than pre-VSG, body weight (35). Together, these observations are consistent with a new defended body weight after RYGB and VSG, but the mechanisms involved are unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this subject

- Gastric bypass surgery leads to a sustained reduction of body weight and fat mass, but the mechanisms are unknown.
- Rats that are weight-reduced by caloric restriction at 3 months after sleeve gastrectomy promptly increase food intake and return to pre-perturbation levels of body weight. Conversely, semi-chronic blockade of brain melanocortin receptor-4 signaling in rats with RYGB increases food intake and body weight in a reversible fashion.
- Together, these observations suggest that the sustained body weight loss after RYGB and VSG is not due to restriction of energy intake, but rather a change in defended body weight level.

What does this study add

- In a new, improved mouse model of RYGB, we demonstrate that RYGB-induced weight loss and fat mass loss is proportional to pre-surgical adiposity, with moderately obese mice losing less body weight and fat compared with very obese mice.
- Remarkably, mice that were weight-reduced to the level of chow controls before surgery, immediately gained weight after surgery, exclusively accounted for by lean mass gain.
- The results provide additional evidence for re-programming of a new body weight set point as an important general mechanism by which RYGB lastingly suppresses body weight.

Fig. 1.

Effect of RYGB in mice with different starting body weight. Mice exposed to a high-fat diet for 12–14 weeks were assigned to 4 groups based on body weight and fat mass and subjected to either RYGB (RYGB high, filled circle, $n = 8$; RYGB medium, open circle ($n = 8$; RYGB low, filled triangle, $n = 8$), or sham surgery (see text). An additional group of mice exposed to high-fat diet for 12 weeks was weight-reduced by calorie restriction before RYGB (RYGB Reduced, open triangle, $n = 4$) or sham surgery (see text). One group of mice

fed regular chow throughout and without surgery (Chow, filled square, $n = 6$) served as additional control.

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Fig. 2.

Effect of RYGB in mice with different starting body weight (high, $n = 8$; medium, $n = 8$; low, $n = 8$) on body weight loss (A), fat mass loss (B), lean mass loss (C), and adiposity index (D, see methods for definition). Bars that do not share the same letters are significantly different from each other ($p < 0.05$, based on ANOVA, followed by Bonferroni-corrected multiple comparison tests).

Fig. 3. Body weight before surgery as predictor of RYGB-induced absolute (A) and relative (B) body weight loss, fat mass loss (C), lean mass loss (D), change in adiposity index (E), and relative excess body weight loss (F, see methods for definition). Note that RYGB Reduced mice shown in Fig. 1 are not included.

Fig. 4.

Paradoxical body weight gain after RYGB in weight-reduced mice. Mice exposed to high-fat diet for 12 weeks were weight-reduced by calorie restriction for 3 weeks before surgery (RYGB, n = 5–7) or sham surgery (Sham, n = 2–6). Immediately after RYGB, body weight (A) increased due to increased lean mass (D) but not fat mass (C). The change in lean mass also resulted in significant changes of adiposity index (E) and relative leanness (F). Absolute (G) and relative (H) fluid mass are also shown. * p < 0.05, before vs. after RYGB.