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Physiological mechanisms behind RYGB surgery

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Abstract

Obesity and its related comorbidities can be detrimental for the affected individual, and challenge public health systems worldwide. Currently, the only available treatment options leading to clinically significant and maintained body weight loss and reduction in obesity related morbidity and mortality are based on surgical interventions. Apart from the “gold standard” Roux-en-Y gastric bypass (RYGB), the vertical sleeve gastrectomy (VSG) and gastric banding (GB) are two frequently performed procedures. This review will discuss animal experiments designed to understand the underlying mechanisms of body weight loss after bariatric surgery. While caloric malabsorption and mechanical restriction are not major factors in this respect, alterations in gut hormone levels are invariably found after RYGB. However, their causal role in RYGB effects on eating and body weight has recently been challenged. Other potential factors contributing to the RYGB effects include increased bile acid concentrations and an altered composition of gut microbiota. RYGB is further associated with remarkable changes in preference for different dietary components such as a decrease in the preference for high fat or sugar; it is important to note that the contribution of altered food preferences to the RYGB effects on body weight is not clear.

Introduction

The obesity epidemic and its related comorbidities constitute a major challenge for both personal health and public health systems worldwide. The enormous increase in knowledge about the physiological mechanisms controlling eating and body weight contrasts with the lack of available pharmacology based therapies that lead to safe, efficient and long-lasting body weight reductions and an ensuing reduction in obesity related comorbidities. Recent insights into underlying mechanisms of obesity and bariatric surgery have led to promising perspectives in respect to gut hormone based strategies against obesity. However, the best results for maintained weight reduction and improvement of comorbidities are still achieved by bariatric surgery [1-4]. This review aims to summarize key findings in respect to underlying physiological mechanisms of the Roux-en-Y Gastric Bypass (RYGB) procedure which by many is still considered the gold standard in bariatric surgery. Reference will also be made to Vertical Sleeve Gastrectomy (VSG) and to Gastric Banding (GB).

Research with animal models helped to elucidate some of the physiological mechanisms that potentially underlie the treatment success of bariatric surgery. Figure 1 illustrates schematically the pre- and postoperative anatomy of the gastrointestinal tract after RYGB and VSG operations in rats. Both operations reduce eating at least temporarily and may increase energy expenditure. Both procedures further lead to changes in food preferences. The majority of data collected with the help of preclinical studies seems to be consistent with findings in humans. However, increases in energy expenditure after RYGB seem to be less consistent in humans when compared to most animal models; this may be related to the much larger heterogeneity of study populations in humans compared to laboratory animals.

Current research often focuses on altered concentrations of gut hormones like glucagon-like peptide-1 (GLP-1) or peptide YY (PYY) and metabolites that per se are known to affect eating and to modulate nutrient metabolism. It needs to be pointed out, however, that association and causality must not be confounded because measurable changes in circulating parameters after bariatric surgery do not necessarily play a causal role for the

observed effects of bariatric surgery; hence, it is not yet clear whether these changes are necessary or sufficient for reduced eating or body weight.

Effects of RYGB on body weight

RYGB in rats or mice leads to a rapid and marked decrease in body weight compared to sham-operated animals (e.g. [5-7]). RYGB operated rats typically lose about 20% of their pre-surgical body weight which then plateaus at a constant level; in some studies, body weight is slowly regained over time, but without ever reaching the body weight of respective control animals. A decrease in body fat mass largely accounts for the decrease in body weight, while lean body mass is typically preserved.

Theoretically, body weight loss after RYGB in comparison to sham-operated controls can be explained by reduced calorie intake, increased energy expenditure, reduced nutrient availability (e.g. caloric malabsorption), altered metabolic efficiency or by a combination of all these factors. Considering the available literature, reduced eating and increased energy expenditure may play a much greater role after RYGB surgery than caloric malabsorption which seems to be only of minor importance for the observed effects of RYGB [5, 8]. Thus, even though the gastrointestinal anatomy is significantly rearranged after RYGB and even though the stomach, duodenum and proximal jejunum are excluded from the flow of ingested food, it seems that the total digestive and absorptive capacity of the small bowel still suffices to avoid maldigestion and subsequent caloric malabsorption. This may at least partly be due to the massive hypertrophy of the small bowel that is observed predominantly in those gut segments that are still in contact with nutrients (i.e. alimentary limb and common channel; see Figure 1) [5, 9, 10]. It must be noted, however, that the contribution of malabsorption to the RYGB induced body weight loss may increase if animals are maintained on a high fat diet [11]. Similarly, in our own laboratory, temporary malabsorption may occasionally be observed under conditions of high fat feeding (e.g. 60% fat by calories), but the contribution to body weight loss seemed to be minor.

Figure 2 indicates that reduced eating is one, but clearly not the only factor contributing to body weight reduction after RYGB in rats. RYGB rats spontaneously eat less after surgery when compared to sham-operated controls; however, sham-operated rats that are pair-fed to RYGB rats have a greater body weight than ad libitum fed RYGB rats. Only if sham-operated rats undergo more severe food restriction and get less food offered than RYGB rats, they show a body weight trajectory that is comparable to RYGB rats. As caloric malabsorption has been shown to only play a minor role [5], RYGB rats may thus have increased energy expenditure, at least compared to body weight matched controls (see below).

Effect of RYGB on food intake and meal pattern

One important factor that contributes to body weight loss after RYGB is a reduction in overall food intake; the reduction in eating seems to be a voluntary process since studies in humans have shown that pre-meal hunger is not higher and post-meal satiation is not lower after RYGB despite an overall lower food intake [12, 13]. In most published studies, RYGB leads to a significant reduction in eating compared to ad libitum fed sham-operated rats. RYGB rats typically eat less during the dark phase of the light/dark cycle and during an entire 24h period; interestingly, light phase food intake is increased in at least some studies (see also Figure 3; [5]).

The reduction in overall food intake is accompanied by a typical change in meal pattern [5, 6, 14]. Interestingly, meal pattern changes in rodent models of RYGB resemble those seen in RYGB patients. Both, patients and rats seem to eat and drink less and on average ingest smaller meals that are consumed with slower eating rates after RYGB surgery.

Simultaneously, the meal frequency increases after RYGB, which however does not compensate for the reduced meal size. Similarities in meal patterns between humans and rats after RYGB suggest that the physiological effects of RYGB may rather rely on altered feedback signals from the gastrointestinal tract to control centers of eating in the brain than on (confounding) psychosocial influences, including dietary counseling.

Interestingly, RYGB rats consume smaller meals in the dark phase, but larger meals in the light phase when compared to sham-operated control rats. As a result, RYGB rats have approximately the same meal size during the dark and light phase while sham-operated rats consume significantly more food per meal during the dark phase than during the light phase. Furthermore, RYGB rats consume significantly more meals during 24 hours than sham-operated rats (Figure 3).

At first sight, one could argue that an overall increase in meal frequency together with a constant meal size indicate the inability of RYGB rats to overcome a mechanical constraint executed by a small gastric pouch; in other words, these compensatory mechanisms may be necessary to overcome mechanical restriction in order to achieve an acceptable level of total caloric intake. Several important findings argue against this interpretation. Firstly, both humans and rats do not increase their water intake with the meal suggesting that there is no attempt to overcome mechanical constraint through food dilution with water. Secondly, there is no correlation between the size of the gastrojejunal anastomosis and weight loss in RYGB rats [15]. Thirdly, blocking the pleotrophic gut hormone response in humans after RYGB with a somatostatin analogue (which does not change the size of the gastric pouch or stoma) can almost double ad libitum food intake [12]; similar effects are seen in rats [16]. Further, if mechanical restriction were a major factor, one would assume that RYGB animals are more hungry than sham-operated animals and try to ingest calorically dense food to overcome the volume restriction; however, the exact opposite is the case because RYGB reduces high fat diet intake relative to low fat intake (e.g., [6, 17]). Finally, if mechanical constraint were an important factor then it should be impossible to exceed the maximal limit. Thus, we food-restricted a group of RYGB rats such that they received less than half of their ad libitum food intake over about two weeks with subsequent unlimited access to solid, normal chow; RYGB rats increased their food intake as soon as ad libitum food was available. Instead of returning to the level of food intake seen in the ad libitum fed RYGB rats, the food-restricted RYGB rats ate significantly more and food intake even exceeded that of sham-operated ad libitum fed rats (Figure 4). Similarly, Stefater and colleagues have shown that temporary restriction

of food access lowers body weight in VSG and control animals; when returning to an ad libitum feeding regimen, all animals, including the VSG rats, overate to compensate for the restriction period and caught up to their pre-restriction body weight in a similar time frame [18]. Overall, these data indicate that it appears unlikely that mechanical constraint is a major factor of reduced eating and the altered meal pattern after RYGB, but also VSG, because there does not seem to be a ceiling effect at the typical level of ad libitum food intake after RYGB or VSG, respectively.

RYGB changes the gut morphology in specific gut segments

The RYGB procedure is associated with typical changes in morphology of intestinal mucosa (e.g., [5, 9, 10, 19]). This has most consistently been described in RYGB rats and the phenomenon seems to be less marked in RYGB mice. In rats, total length of the small intestine remains unaltered, but a marked increase in wet weight of the small intestine indicates segmental hypertrophy after RYGB. Specifically, muscular and mucosal layers are significantly thicker in the alimentary (Roux) limb after RYGB in comparison with corresponding intestinal segments in sham-operated controls; both mucosal crypt depth and villi height increased. Depending on the dimensions of the various limbs after RYGB [5, 9, 10], similar changes may also be observed in the common channel of some RYGB models, but not in the biliopancreatic limb.

The underlying mechanisms leading to hypertrophy of the intestinal mucosa including muscle layers remain unknown. Mechanical or chemical factors or a combination of both may be involved. It is however intriguing that not all intestinal segments show a hypertrophic response. One possible explanation is linked to an increased release of GLP-2 from intestinal L-cells ([19]; see also below) facilitating intestinal hypertrophy in conjunction with intraluminal factors such as stimulation by nutrients. Overall, it may be postulated that hypertrophy of certain intestinal segments in RYGB animals represents an adaptive response to optimize nutrient digestion and absorption under conditions where nutrients and

digestive juices from the pancreas and liver mix more distally than under physiological conditions. Similar responses can be seen in experiments where segments of the small intestine have been surgically removed.

Because of the potential importance of gut hormones for the beneficial effects of RYGB and other types of bariatric surgery, several groups also investigated whether RYGB modifies the distribution or density of enteroendocrine cells in the gastrointestinal tract. Consistent with the general hypertrophy of the intestinal mucosa, there are clear indications for an adaptive increase in the number of endocrine cells. This translates into an increase in the absolute number of L-cells releasing GLP-1, GLP-2 and PYY, and of cholecystokinin (CCK) immunoreactive cells; while major effects were seen in the alimentary limb and the common channel, no changes were observed in the biliopancreatic limb. Interestingly, however, regional density of enteroendocrine cells remains unaltered [9, 20].

When testing the specific expression of preproglucagon (for GLP-1) and PYY in the intestinal segments, the mRNA expression per cell is only increased in the common channel, but not in the alimentary limb [20]; hence, it seems that both the (general) stimulus that leads to intestinal hypertrophy (perhaps induced by increased GLP-2 secretions) and the presence of nutrients plus bile acids, gastric and pancreatic juices may be necessary to increase gastrointestinal hormone production at the level of individual cells. Overall, data clearly indicate that the hormonal secretory capacity of the small intestine increases after RYGB. Further, L-cell density seems to increase along the rostro-caudal axis. Importantly, however, it must be noted that the majority of the total number of L-cells is found in more proximal gut segments, and not in the ileum, after RYGB surgery in rats [20].

RYGB surgery changes the concentration of circulating gut hormones

One of the most consistent findings and one of the most frequently proposed mechanisms contributing to reduced eating and body weight after RYGB surgery is the increased

secretion of gut hormones, in particular the L-cell products GLP-1 and PYY, but also amylin and CCK [12, 13, 19, 21, 22]. The single or combined action of these satiating hormones provides a plausible explanation for the decrease in meal size observed in RYGB rats. The blood concentration of ghrelin, in contrast, seems to decrease after RYGB which theoretically could be associated with a reduced drive to eat; however, data about changes in circulating ghrelin are rather inconsistent [13, 21, 23, 24] and the relevance of changes in ghrelin secretion, if they occur, is also unclear. Further, it is unclear whether the observed changes in ghrelin concentrations observed in some studies are physiologically relevant modulators of eating; and finally, ghrelin deficient mice showed an unaltered body weight lowering response to the VSG procedure [25].

The idea that blood borne factors play an important role for post-RYGB physiology is based on seminal experiments by Atkinson and colleagues who showed that the injection of plasma collected postprandially from rats with an intestinal bypass reduces eating in recipient rats compared to rats receiving postprandial plasma from sham-operated controls. This effect was not seen if plasma from fasted bypass or sham-operated animals, respectively, was injected to recipient rats [26]. A large number of subsequent studies provided evidence for a potential role of increased secretion of satiating gut hormones for RYGB surgery effects (e.g., [13, 19, 21, 27]). Most of the available data provide correlational evidence, while data indicating causality are still scarce. The general belief is that RYGB surgery changes nutrient fluxes in such a way that an increased secretory stimulus to enteroendocrine cells results in increased blood levels of gastrointestinal satiation hormones, including GLP-1, PYY, amylin and CCK. The effect refers in particular to postprandial concentrations of these hormones, but at least in some studies, the basal concentrations of these hormones are also increased; the (physiological) relevance of increased basal levels for the control of eating, however, is not clear.

Consistent with the idea of an important role of increased gut hormone secretion after RYGB are experiments in humans and rats showing that blockade of gut hormone release with

somatostatin analogues increases eating in RYGB patients or rats, respectively [12, 16]. Further, RYGB patients clustered into a group of “good responders” (with a body weight loss over approximately two years of about 40%) had a significantly better postprandial GLP-1 and PYY response than patients being classified as “poor responders” (with less than 20% body weight loss; [12]).

At present the stimuli leading to increased secretions of gut hormones are unknown and various hypotheses have been raised. As discussed above, the general capacity to release gut hormones seems to increase markedly as a result of the hypertrophy of the small intestinal mucosa [5, 9, 10, 19]. However, elevated gut hormones can already be observed within few days after surgery, i.e. at a time when this hypertrophic response presumably is still negligible. One possibility discussed frequently is the higher concentration of nutrients in distal segments of the small intestine. Considering the findings discussed above that the total number of L-cells is actually much higher in more proximal small intestinal segments (hence in the alimentary limb of RYGB animals), undiluted nutrients in the alimentary limb may also well be responsible for higher secretions of GLP-1, PYY and perhaps CCK. Additionally, undiluted bile acid secretions reaching the common limb via the biliopancreatic limb of RYGB animals may play an important role because it is well documented that luminal bile acids directly stimulate L-cell secretion [28, 29]. At present, it is however unclear if the increased expression of preproglucagon and PYY and secretion of GLP-1 and PYY are directly linked to an increased delivery of bile acids to L-cells in the common channel; this has not yet been studied and compared between RYGB and sham-operated rats. Unfortunately, specific antagonists of the bile acid receptor (TGR5, also called GPBAR1 [G protein-coupled bile acid receptor 1]) that mediates increased L-cell secretions [28, 29] are not available and to our knowledge, respective experiments with RYGB operated TGR5 knockout mice have not been performed yet.

Another open question is how increased basal and postprandial amylin secretion is triggered in RYGB rats [21]. It seems unlikely that a direct effect of glucose (or other metabolites of

carbohydrate metabolism) at the pancreatic beta-cell plays a role because glucose concentrations are either unchanged or rather decrease (in diabetic individuals) after RYGB. Increased amylin levels may be caused by a stimulating effect of GLP-1 on beta-cell secretion but this has so far not been tested. Given the therapeutic potential of amylin as an anti-obesity treatment [30, 31], it will be interesting to study the causal contribution of amylin to reduced eating [32], body weight [33, 34] and increased energy expenditure [35, 36] after RYGB.

Increased secretions of GLP-1 and PYY are also typical observations after VSG (e.g., [8, 37, 38]); similar to RYGB, this fueled the idea that the eating inhibitory effect of VSG may at least in part depend on the elevated postprandial gut hormone levels [37].

Causal role of elevated GLP-1 and PYY levels in the treatment success of RYGB surgery

The association between elevated concentrations of gut hormones like GLP-1, PYY, CCK and amylin on one side and reduced eating after RYGB on the other side is compelling. However, the evidence for a causal role of these gut hormones in reduced eating is surprisingly limited. Le Roux and colleagues [13] have shown that acute pre-treatment with a PYY specific antiserum can reverse the effect of bypass on eating in rats, and Chandarana and colleagues [39] have shown that PYY knockout mice do not lose body weight after bypass surgery. It needs to be mentioned that the surgical procedures in both studies did not correspond to the true RYGB procedure as it is currently performed in human patients.

Our own data with acute blockade of the GLP-1 receptor are inconsistent. Acute administration of the GLP-1 receptor antagonist exendin-9 increased eating only in RYGB, but not in sham-operated male rats [40]; this potentially indicates that GLP-1 receptor blockade reverses the effect of (exaggerated) GLP-1 levels in RYGB rats. On the other hand, exendin-9 increased intake of a test meal in female rats after both sham- and RYGB

operation to a similar extent questioning a role of higher GLP-1 levels in RYGB rats, at least as a single factor [41]; findings were similar when using a CCK receptor antagonist. Further, recently published data in two different models of whole body GLP-1 receptor knockout mice indicated that the GLP-1 receptor does not seem to be necessary for most effects induced by VSG because knockout and wildtype animals showed very similar responses to the VSG procedure [42].

Overall, it must be stated that the causal contribution of elevated gut hormone secretions to the beneficial effects of bariatric surgery procedures may be less clear than originally postulated. This is at least true in cases where the contribution of single hormones has been tested. Obviously, the RYGB procedure (but also the VSG procedure) leads to an entire cocktail of changes in the concentrations of many different factors so that the manipulation of single aspects (like the use of single knockout models) may be unable to mimic the true situation post-bariatric surgery.

There is an apparent discrepancy between studies suggesting that blockade of the GLP-1 receptor by specific antagonists prevents improvement in glucose homeostasis after VSG [37, 38] and studies that question an important role of the GLP-1 receptor by using GLP-1 receptor knockout mice [42]. Such conflicting results should put an additional note of caution on precautionous conclusions. Each experimental procedure and model bears its advantages and disadvantages and data must be interpreted with care and objectivity; especially because the literature does provide multiple pieces of evidence suggesting that gut hormones like GLP-1 are indeed important factors for the improvement of glucose metabolism after RYGB, VSG and other types of bariatric or metabolic surgery (e.g., [2, 7, 37, 38, 43]).

Extension of RYGB's effect on eating by administration of exogenous gut hormones

Even though the average reduction in body weight after RYGB is impressive, not all patients lose similar amounts of excessive weight, and some may even regain most of their body weight that was lost initially. Hence, supportive therapy options may be needed, particularly in patients whose body weight loss is less than expected or metabolically needed. The currently available supportive therapy options are rather limited and although revisional surgery in principle is possible (e.g. to further reduce the size of the gastric pouch or to shorten the length of the common channel), re-dos can be technically very demanding and are associated with a higher complication rate compared to primary operations. Thus, non-surgical options need to be explored that may help to reach the expected goals.

Recent studies investigated the effect of exogenously administered PYY and the GLP-1 agonist exendin-4 on eating in RYGB rats [16, 40]. RYGB led to the expected decrease in eating, but it was important to see that RYGB rats are still fully responsive to PYY and exendin-4 administration; both peptides reduced eating significantly in RYGB and sham-operated rats; the degree of food intake reduction was comparable or even higher [40]. In other words, despite the increase in basal and postprandial GLP-1 and PYY levels, RYGB rats retain sensitivity to the action of these hormones or their agonists, respectively; hence, there is no indication of a desensitization of the respective receptor systems. Based on these short term experiments, it will be interesting to test whether chronic administration of PYY, GLP-1 or their analogues also lead to a sustained reduction of eating and decrease in body weight under conditions when the effect of bariatric surgery per se is relatively minor; similar studies should include amylin [31].

RYGB surgery changes the concentration of circulating bile acids

As mentioned before, elevated levels of circulating bile acids are also a very typical finding after RYGB and some other surgical procedures like ileal interposition (e.g. [44-47]). It has been therefore hypothesized that increased bile acid levels may be linked to the metabolic

improvement after RYGB as bile acids have been suggested to directly affect carbohydrate and lipid metabolism, as well as potentially energy expenditure via the (intracellular) bile acid receptor FXR. In our own studies, we observed a clear increase in fasting levels of circulating bile as soon as 8 days post-RYGB in rats (Figure 5), but also at later time points in diabetic ZDF rats. Data indicating that the intracellular bile acid receptor FXR may be necessary for bariatric surgery induced effects on body weight, glucose and lipid metabolism have been presented at various scientific meetings, but to our knowledge, no such data have been published yet.

RYGB and gut microbiota

Gut microbiota have been identified as important modulators of whole body energy metabolism [48, 49] and they have been claimed to play a causal role in the development (or maintenance) of obesity under different feeding conditions [48]. Interestingly, several studies show that the composition of gut microbiota is altered by RYGB [45, 50, 51] and that this effect may be causally linked to a reduction in the low-grade inflammatory state that follows the reduction in body weight [51]. Changes in gut microbiota seem to be comparable in rodents and humans and may in fact not be related to the RYGB induced changes in eating or body weight, but to the surgical procedure per se [50]. Further, changes in gut microbiota composition may play a causal role in the body weight effects of RYGB surgery, because transfer of gut microbiota from RYGB mice to germ free mice reduced their body weight compared to mice that received gut microbiota from sham-operated mice [50].

Because gut microbiota heavily influence bile acid metabolism [52], it will be important to test whether alterations in gut microbiota are causally involved in altered bile acid metabolism after RYGB, and whether the latter is necessary for beneficial effects of RYGB (or other bariatric surgery procedures, respectively; [2, 3, 43]) on insulin sensitivity and whole body energy metabolism.

Changes in energy expenditure after RYGB surgery

In animal models of RYGB, spontaneous food intake is typically reduced in comparison to ad libitum fed sham-operated controls. However, lower food intake in RYGB rats can only explain part of the body weight loss; sham-operated rats that are weight-matched to RYGB require up to 40% less food than RYGB rats to maintain a similar level of body weight (Figure 2). As other potential explanations such as caloric malabsorption (at least when animals are fed standard chow diets; but see [11]) or an increased inflammatory state after the surgery have been shown to be either negligible or absent, energy expenditure after RYGB seems to be higher than in respective control animals of similar body weight [5, 7, 8, 53, 54].

In fact, we and a number of other laboratories reported that body weight loss in rats after RYGB is not associated with the decrease in energy expenditure that can be usually observed with traditional weight loss strategies such as food restriction or dieting, respectively [5-7]. When energy expenditure determined by indirect calorimetry is corrected for body weight, energy expenditure is higher in RYGB rats than in sham-operated ad libitum fed and weight matched controls. However, when calculating total energy expenditure (i.e. uncorrected for body weight), energy expenditure is not consistently increased after RYGB; importantly, the comparison to the weight matched controls is always positive, after both calculations. Thus, RYGB prevents the (expected) decrease in energy expenditure subsequent to body weight loss. This fact may well contribute to the long-term maintenance of reduced body weight after RYGB operations in humans. In some but not all studies, the change in energy expenditure is paralleled by a lower respiratory quotient indicating that fat oxidation is increased over carbohydrate oxidation. However, the latter may be rather related to body weight loss than representing a specific surgical effect as body weight matched sham-operated controls show a similar response.

In contrast to preclinical studies in rats, the human literature is not entirely consistent in respect to RYGB induced changes in energy expenditure [53, 55-59]. Some but not all

studies report increases in energy expenditure, but energy expenditure was often measured only over short time periods and then extrapolated to a 24h period in most cases; hence, true effects induced by RYGB may have been overlooked. Further, necessary control groups were not always included in the studies.

At present, mechanisms underlying altered energy expenditure after RYGB remain unclear. It seems that neither increased spontaneous physical activity nor higher body temperature can explain these findings as core body temperature was rather lower after RYGB (but also in weight matched controls). However, heat dissipation was not assessed separately [5]. In a recent study, brown adipose tissue activity remained unaltered after RYGB which is consistent with the lack of increased core body temperature [5, 60]. Other factors like altered energy efficiency of skeletal muscle have so far not been tested.

In our own experiments, we found that RYGB rats showed a slightly higher core temperature during the light phase when compared to weight-matched sham-operated controls which might have been due to increased food consumption and hence differences in diet-induced thermogenesis. In fact, diet-induced thermogenesis in response to a 5 g test meal was higher after RYGB than in body weight-matched control animals. Similarly, postprandial energy expenditure was also higher in human RYGB patients compared to patients receiving vertical banded gastroplasty (VBG; [56]).

Because RYGB, but not VBG increases postprandial levels of GLP-1 and because GLP-1 and other products of the pre-proglucagon gene (e.g. oxyntomodulin) have been implicated in the control of energy expenditure, we recently tested whether acute modulation of the GLP-1 system influences the RYGB induced changes in energy expenditure. We found however that neither acute stimulation nor blockade of GLP-1 receptors with exendin-4 or exendin-9, respectively, influences energy expenditure in any group; in other words, energy expenditure was higher after RYGB than sham operation, but remained unaltered by the manipulation of the GLP-1 system [40].

The increase in total energy expenditure in RYGB rats may also be explained by a higher energy requirement due to the massively hypertrophied small intestine [5, 9, 10]. The entire small bowel increased its total weight by approximately 75% after RYGB; as small intestinal oxygen consumption has been estimated to make up for about 20% of total oxygen consumption [61], gut hypertrophy may at least partly explain the higher energy requirement that, ultimately, may contribute to maintenance of body weight loss.

Central nervous system (CNS) contribution to the eating inhibitory effects of RYGB

Studies about changes in CNS signaling after RYGB are rare. Even though peripheral signals potentially mediating RYGB induced effects have not been completely identified, it is clear that any signal inducing changes on eating behavior and probably also on energy expenditure needs to be transmitted to the brain. Such signals may be transferred to the brain either via vagal or non-vagal afferent nerve signaling or directly via blood circulation. A recent study has shown that the eating inhibitory effect and subsequent body weight loss after RYGB seems to depend at least in part on vagal transmission because both effects are more pronounced when part of the subdiaphragmatic vagal innervation (specifically the para-esophageal neurovascular bundle) is preserved during RYGB surgery [15]. Further, the decreased excitability of vagal efferent neurons in the dorsal motor nucleus of the vagus that results from diet induced obesity can be reversed by RYGB in rats [62]; this is accompanied by an improved response of these neurons to CCK and GLP-1. Yet, another study indicated that at least for the short term result, vagal dissection may actually increase the effects of RYGB on body weight; yet, the long term outcome did not differ between vagotomized and control RYGB rats [63]. Further, RYGB effects seem to be independent of the specific vagal innervation of the portal vein and liver [54]. Given the somewhat contradictory findings about the role of the vagus in RYGB, it will be important to study the specific role of other vagal fibres in more detail.

Remarkably little is known about specific effects of RYGB (or other bariatric surgery procedures) on the CNS centers that are involved in eating control; most of the recent studies examined the role of the melanocortin system given its overall importance in the control of eating and body weight [64-71]. Unexplained species difference may be present; while homo- and heterozygous melanocortin-4 receptor (MC4r) knockout rats appear to be fully responsive to weight reducing VSG surgery [71], homozygous MC4r knockout mice lose less weight after RYGB than heterozygous knockout or wildtype mice [67]. The sufficiency of one functional MC4r gene was also confirmed in some studies including RYGB or VSG operated humans [66, 67, 71]. The important role of the melanocortin system is further supported by findings in humans with a specific variant of the MC4 gene [MC4r(I251L)] which is associated with a better metabolic status; in fact, carriers of this variant have improved surgery outcome [68, 70].

An elegant study recently described potential sites of MC4 signaling for some of the observed RYGB effects; RYGB was performed in an animal model of DIO mice. In these mice, the RYGB induced body weight loss is mainly due to an increase in energy expenditure; the mice are also characterized by improved insulin sensitivity mainly in the liver, but not skeletal muscle or adipose tissue. Most of these effects were absent in MC4r knockout mice, but similar to the study described above with complete MC4r knockouts [67], one functional allele was sufficient to rescue the effect of RYGB [70]; this study clearly shows that functional MC4 receptors are required for the effects of RYGB on energy expenditure, body weight and glucose metabolism in mice. Interestingly, the genetic re-introduction of the MC4r in key autonomic neurons in the brainstem, including the cholinergic preganglionic motor neurons of the dorsal motor nucleus of the vagus, reinstated the effect of RYGB on insulin sensitivity, but not on body weight or obesity; in the latter respect, the mice behaved like (full) MC4r knockouts. In contrast, the re-introduction of the MC4r in cholinergic preganglionic neurons of both the parasympathetic and the sympathetic system reinstated the RYGB effect on eating, body weight and adiposity; in this case, the improved insulin

sensitivity was only secondary to weight loss [70]. Hence, different populations of MC4r's seem to be critical for the mediation of specific aspects of RYGB surgery.

Concluding remarks

Obesity and its related comorbidities are detrimental diseases for the affected individual, and they remain major challenges to public health systems worldwide. The only currently available treatment options that lead to a clinically significant and long-lasting body weight loss and a reduction in obesity related morbidity and mortality are based on surgical interventions [2-4]. Apart from the "gold standard" Roux-en-Y gastric bypass (RYGB), the vertical sleeve gastrectomy (VSG) and the gastric banding (GB) are two frequently performed procedures. While the so-called restrictive GB procedure predominantly works by mechanical means, the RYGB and VSG related effects have been linked to similar changes in circulating levels of gastrointestinal hormones or bile acids [8, 72, 73]. Most studies, however, also point out some differences and suggest that RYGB influences eating and energy expenditure, while VSG seems to reduce body weight mainly by an effect on eating. Despite enormous progress in the field, the number of studies linking these changes in a causal manner is still relatively small and more work needs to be done to determine the necessity of many of the observed effects for the success of bariatric surgery. Similarly, even though many studies have reported alterations in food preferences after RYGB and VSG (reviewed in [74]; see also [17, 75-82]; but see [73]), the necessity of these changes for the successful body weight loss after RYGB or VSG is far from clear.

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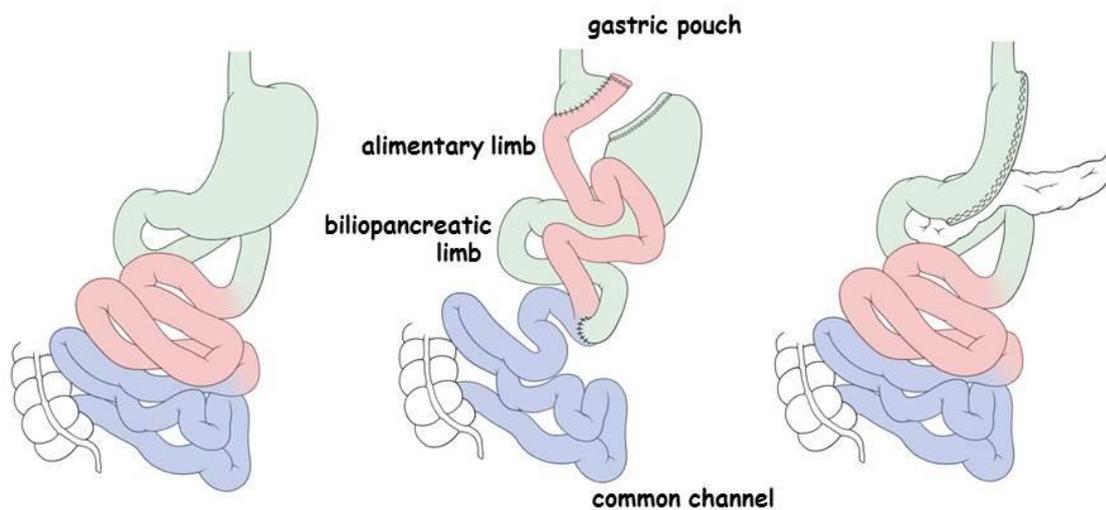
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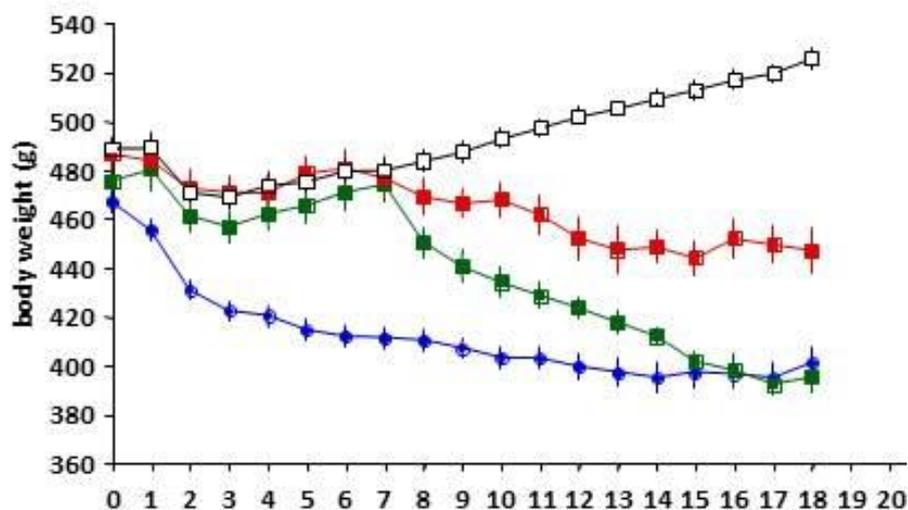
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Figure 1



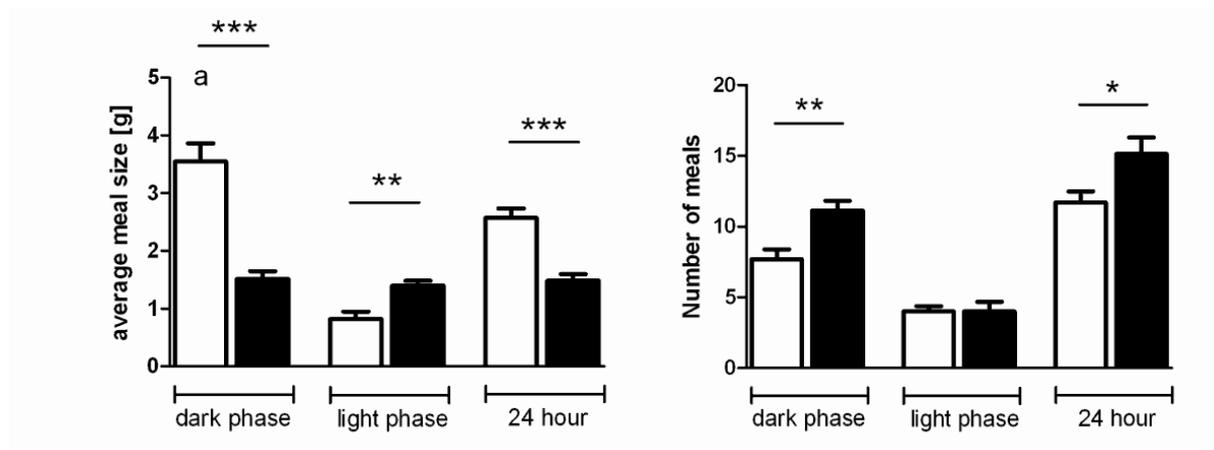
Schematic representation of the sham-operation (left), the Roux-en-Y gastric bypass (RYGB; middle) and the vertical sleeve gastrectomy (VSG; right) in rats. In our laboratory, the different segments of the small intestine after the RYGB operation in rats have the following approximate dimensions: biliopancreatic limb 10 cm (green); alimentary limb (Roux limb) 50 cm (red); common channel 25 cm (blue). The gastric pouch has a volume of < 5 % of the intact stomach.

Figure 2



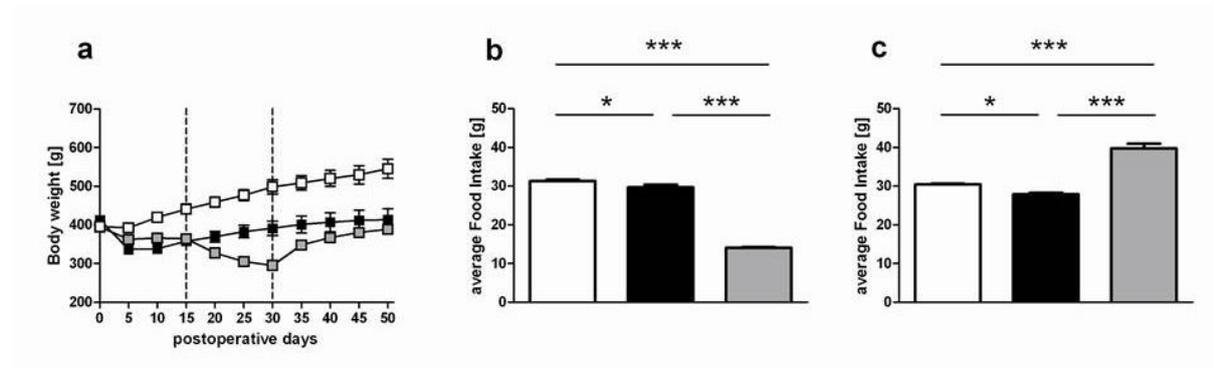
Development of body weight from the day of operation (day 0) in sham-operated rats (squares) and RYGB rats (blue circles). On day 7 after surgery, sham-operated rats were randomized to be fed ad libitum (white squares; average daily food intake approx. 35g), pair fed to the RYGB rats (red squares; average daily food intake approx. 25g) or food restricted to match the rats' body weight to that of RYGB rats (green squares; average daily food intake approx. 8g). Of note, from about 3 weeks after surgery, body weight matched rats received on average about 50% of the amount of food eaten by the ad libitum fed rats to maintain the same body weight as RYGB rats. Data are shown as mean \pm SEM with n = 6–8 per group.

Figure 3



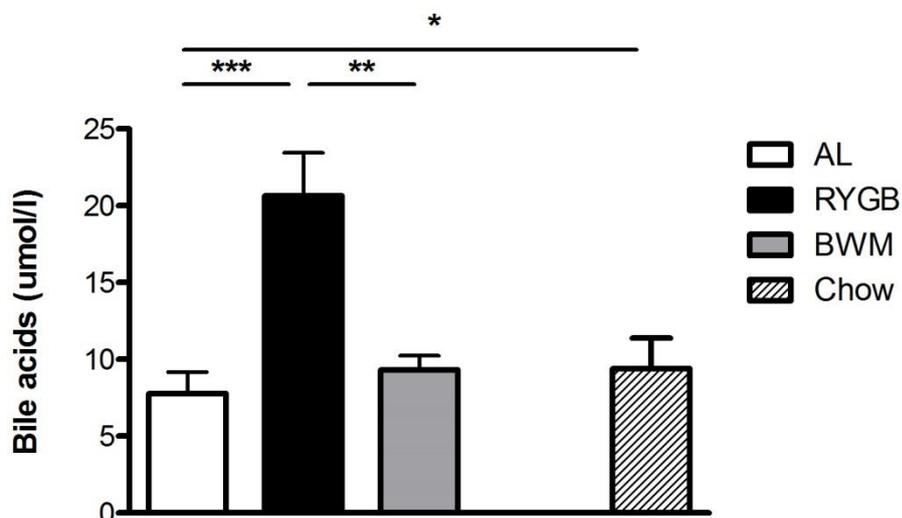
Meal pattern in rats that were sham-operated (white bars) or RYGB operated (black bars). RYGB rats eat smaller but more frequent meals during the dark phase or during an entire 24h period, respectively; during the light phase, meal size slightly increases but meal number does not change. Meal pattern analysis was performed 6-8 weeks postoperatively. Data are shown as mean \pm SEM with $n = 6-8$ per group; *, **, *** significant difference between sham-operated and RYGB rats ($p < 0.05$, $p < 0.01$, $p < 0.001$, respectively).

Figure 4



(a) Body weight in rats that were sham-operated (white squares) or RYGB operated (grey and black squares) on day 0. Between postoperative day 15 and 30, part of the RYGB rats (grey squares) were food restricted to 50% of the food eaten by the ad libitum fed RYGB rats (black squares); average daily food intake from day 15-30 (sham: white bar; RYGB ad libitum: black bar; RYGB restricted: grey bar) is depicted in (b). From day 30, all rats had again ad libitum access to food; average daily food intake between day 30-50 is depicted in (c). Data are shown as mean \pm SEM with $n = 6-8$ per group.

Figure 5



Increased fasting concentrations of circulating total bile acids 8 days after surgery. Rats had been prefed a high fat (60% fat/energy) and high cholesterol (1.25%) diet for 7 weeks before surgery, and rats were maintained on the same diets after surgery. On the day of surgery, sham-operated rats were randomized into rats fed ad libitum (AL; n = 12) or weight matched (BWM; n = 12) to the RYGB (n = 17) rats. For comparison, bile acid levels in age matched chow fed control animals are also shown (n = 6). Bile acids in RYGB rats were significantly higher compared to all other groups. Data are shown as mean \pm SEM with *, **, *** indicating significant differences between the groups ($p < 0.05$, $p < 0.01$, $p < 0.001$, respectively).