Review Article

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Impact of Roux-En-Y Gastric Bypass Surgery on Neurohormonal and Gastrointestinal Physiology: Insights for Future Weight Loss Efforts

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Abstract

Roux-en-Y Gastric Bypass (RYGB), is an effective weight loss intervention for patients failing conventional nonsurgical methods. Despite its popularity, only a subset of patients undergo RYGB due to its cumbersome nature. Furthermore, patients may experience nutritional deficiencies or weight regain after RYGB. This review will delineate the less known impact of RYGB on neurohormonal and gastrointestinal physiology involved in weight loss. Understanding these alterations will contribute to the development of future novel investigations targeting viable weight loss strategies.

Introduction

RYGB is one of the most common bariatric approaches and leads to marked improvements in inflammatory status, insulin resistance, and several metabolically active hormones including leptin and adiponectin [1-7]. These improvements are associated with lower morbidity and mortality even in severely obese patients [8-17].

Therefore, the number of patients undergoing Roux-en-Y gastric bypass (RYGB) surgery has increased by almost tenfold in the past 2 decades, with approximately 101,645 operations performed in 2011 alone [18,19]. However, although RYGB is effective for the vast majority of patients, a small proportion of RYGB patients develop serious nutritional complications, debilitating gastrointestinal (GI) symptoms, and/or fail to reach their weight loss goals [20-25].

Thus, RYGB use decreased in recent years with the increasing application of sleeve gastrectomy as an effective and less cumbersome bariatric approach [26,27]. Furthermore, newer less invasive weight loss interventions, such as intra-gastric balloons for instance, are gaining popularity and may induce weight loss through delayed gastric emptying and humoral changes [28].

As a result, it is important to review the influence of RYGB on neurohormonal and gastrointestinal physiology in order to understand their role in RYGB induced weight loss and ultimately guide future less invasive weight management innovations that can mimic RYGB effect effectively.

Methods

We performed a literature search in PubMed and Medline, using the terms bariatric surgery, gastric bypass, obesity surgery, and Roux-en-Y. These were searched as Medical Subject Headings "MeSH" terms and also as text words.

These individual MeSH term search results and text word search results were all combined using the Boolean operator "OR". The combined search was limited to English language using the language filter. Human and animal studies were included.

This search result was then coupled with secondary search terms in relation to our focus topics using the Boolean operator "AND". The title and abstracts of articles that resulted from this secondary search were screened for relevance in relation to the focus topic. If found relevant, their references were further reviewed to identify additional published studies not indexed in PubMed.

The Roux-en-Y gastric bypass procedure

Four bariatric surgical procedures are commonly performed in the United States and worldwide: 1) RYGB; 2) Adjustable Gastric Banding (AGB); 3) Sleeve Gastrectomy (VSG), and 4) Bilopancreatic Diversion (BPD) with or without duodenal switch (Figure 1).
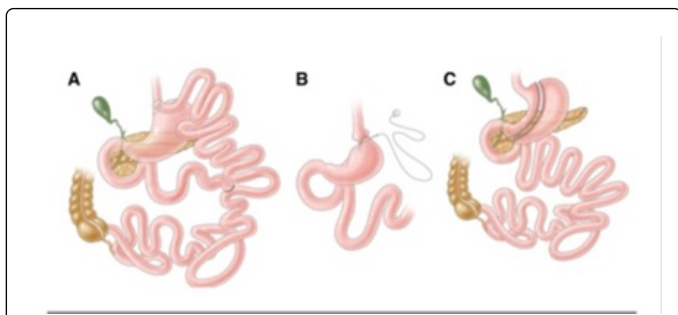
Figure 1: Four types of bariatric surgical procedures, A) RYGB; B) Adjustable Gastric Banding (AGB); C) Sleeve Gastrectomy (SG) and D-Bilopancreatic Diversion (BPD) with or (E) without duodenal switch.

RYGB was introduced in 1967 as a treatment for obesity [29]. The RYGB procedure involves creation of a proximal stomach pouch approximately 30 ml in size. The intestinal jejunum is then transected ~30 cm below the Ligament of Treitz to form the Roux limb.

The distal jejunal segment then forms a gastroenterostomy, while the proximal segment is connected to the small bowel ~100 cm below the jejunal division. Despite a degree of recent standardization, construction of gastric pouches, gastrojejunostomies or the Roux-en-Y limbs all exhibit patient-specific variability [30].

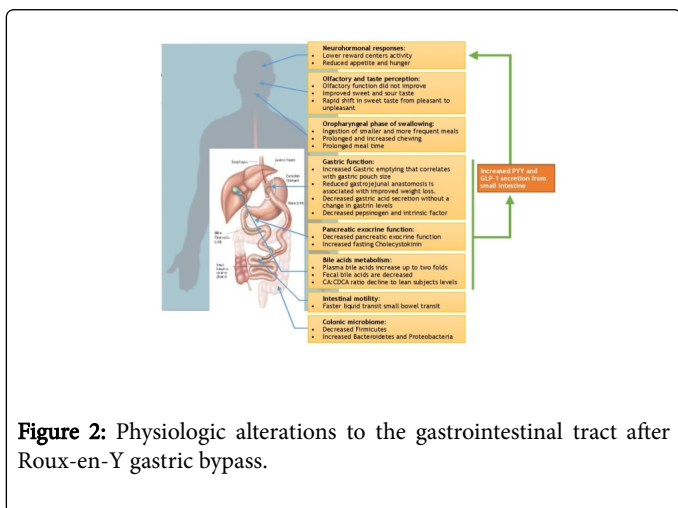Neurohormonal and Gastrointestinal Physiology Alterations after Roux-en-Y gastric bypass (Figure 2)

Figure 2: Physiologic alterations to the gastrointestinal tract after Roux-en-Y gastric bypass.

Feeding behavior and neuro-hormonal changes after RYGB

Functional Magnetic Resonance Imaging (MRI) and positron emission topography (PET) imaging studies have highlighted some of the key neural responses that occur following food intake in lean, obese, and post RYGB patients. Compared to lean controls, pictorial representations of food to obese subjects more intensely activate regions of the frontal, dorsomedial prefrontal, precentral and parahippocampal cortices.

These regions stimulate attention to (and memory of) food as well as enhance food seeking behavior that is associated with weight gain [31,32]. Conversely, dorsolateral prefrontal and insular brain centers

responsible for appetite control are suppressed in obesity, leading to attenuated impulse control [31]. In addition, feeding in obese patients fails to stimulate a 'high reward' response in mesolimbic pathways and culminates in overeating [31,33]. Thus obese patients have a more exaggerated memory of food-associated rewards and augmented food seeking behavior. These neuronal changes lead to reduced appetite control and reward during food ingestion that contributes to excessive caloric intake.

After RYGB surgery, the activity of the mesolimbic reward pathway and other reward centers is reduced in response to food pictures, especially visual representations of high caloric density food. This is associated with a decreased desire to eat [34,35]. Furthermore, RYGB surgery patients have indistinguishable hunger reactions and brain activity to food presentation from lean controls [36]. This indicates a degree of RYGB-induced normalization of obesity-associated food neural impulses.

Peptide YY (PYY) and Glucagon-like peptide-1 (GLP-1), produced by the L cells in the GI tract, may play a critical role in this integrated neural response. They have been shown to act on the central nervous system to modulate appetite and feeding behavior [37-39]. A strong body of evidence indicates that PYY and GLP-1 are suppressed in obese patients and increase after RYGB surgery [40-44]. This increase occurs in a dose dependent manner in relation to dietary calorie content and is likely due to RYGB anatomical changes, as opposed to the subsequent weight loss, as the increase occurs prior to significant weight loss [45-47]. Although less well studied, motilin, a peptide released from the upper intestine, stimulates phase III migrating motor complex and hunger. Morbidly obese patients have higher motilin levels compared to lean controls, and evidence suggests that these levels normalize after gastric bypass surgery [48]. Ghrelin, an orexigenic or appetite-stimulating hormone [49-51], is decreased shortly after RYGB in some studies. However, ghrelin returns to pre-operative levels a few months after surgery despite continued weight loss [52], arguing against its role as a significant contributor to long-term changes in appetite after RYGB surgery.

The summation of these findings suggests 1) that neural responses to food are altered in obesity and appear to be recovered after RYGB surgery, and 2) that this phenomenon may be related to the neurohormonal effects of gastrointestinal incretin hormones. These findings are critically important for future research in obesity pharmacotherapy and emphasize the need further investigation in the future.

Impact of RYGB on olfactory and taste perception and relation to weight loss

Taste and smell are important modulators of feeding behavior and appetite [53,54]. Taste sensation is decreased in obese compared to lean controls, which may partly explain the inhibited reward during food ingestion [55-57]. After RYGB, the acuity for sweet and sour tastes is increased to levels that resemble lean subjects [57,58]. There is also a rapid shift in sweet taste from pleasant to unpleasant after surgery [59], likely due to altered post-surgical neural responses. These changes potentially lead to improved reward response to food or high caloric food aversion after surgery [34,60-62]. Olfactory sense and discrimination is decreased in obese patients, possibly as result of chronic high fat intake associated with obesity [57,63,64]. However, although olfactory function seems to improve after Sleeve Gastrectomy, RYGB does not lead to similar normalization,

irrespective of BMI [57,65,66]. Although incompletely understood, this intriguing finding may be due to more pronounced olfactory dysfunction in RYGB surgery candidates at baseline and/or to unidentified procedure-specific factors. This data suggest that taste may play a role in obesity and weight loss after RYGB.

The oropharyngeal phase of swallowing and weight loss after RYGB

The oropharyngeal phase is stereotyped in humans and starts with solid food transportation to the back of the mouth after ingestion [67]. Then food is processed through mastication cycles in order to soften it and form a bolus suitable for subsequent swallowing [67, 68]. A review of studies evaluating mastication in obese compared to lean patients leads to inconsistent findings. In some reports, obese patients assembled food faster, with less chewing time (CT) and chewing cycles (CC) [69,70]. However, two additional studies showed either increased or unchanged CC and CT in obese patients [71,72]. This variation could be due to sample size and study design. After RYGB surgery, patients ingest smaller and more frequent meals [73,74] and solid food mastication CC and CTs are increased [75]. Meal ingestion time is also prolonged [76]. The prolonged eating rate and chewing seen in RYGB can contribute to its positive impact on satiety [77]. It's noteworthy that improved mastication was thought to contribute to efficacy of other obesity treatments such as aspiration therapy [77,78].

Gastric function after RYGB and impact on weight loss

Significant digestion of macronutrients occurs in the stomach. With accelerated emptying, gastric retention is decreased after RYGB [79-85]. In a recent study, using Scintigraphy and 3DCT, accelerated gastric emptying was found to correlate with small volume of gastric pouch and lower risk of weight regain after RYGB [86]. This accelerated gastric emptying potenitally enhances the postprandial insulin response seen after RYGB, and may be partially responsible for the augmented release of GLP-1 and PYY [84, 85]. Reduction of gastrojejunal anastomosis size was also associated with better weight loss maintenance after RYGB, however underlying mechanisms are not completely understood [87]. After bariatric surgery, baseline and peak gastric acid secretion from the excluded stomach remnant is reduced, with no change in fasting and post-prandial gastrin levels [88-92]. The change gastric acid secretion may affect PYY levels after RYGB surgery and subsequent weight loss [93]. Postprandial intrinsic factor and pepsinogen secretion is also substantially decreased [91,94]. In summary, the increased gastric emptying and decreased secretion are important factors in post-RYGB weight loss and may account for the augmented release of GLP-1 and PYY after RYGB.

Pancreatic exocrine function after RYGB and impact on malabsorption and satiety

Fecal elastase-1 is reduced 8 months post-RYGB as opposed to obese controls [95]. In parallel, patients who undergo RYGB exhibit lower trypsin, chymotrypsin and amylase soon after surgery [96-98]. The decreased pancreatic exocrine function could be due to surgical alteration and can be responsible for the activation of PYY and the mild fatty acids malabsorption seen after RYGB [98]. This led to techniques promoting malabsorption such as the EndoBarrier (GI Dynamics, Lexington, MA, USA) and the incision less magnetic anastomosis system (IMAS) [99,100]. Cholecystokinin (CCK) is secreted from I cells in the duodenum and jejunum in the presence of

duodenal lipids. It affects gallbladder contraction and pancreatic enzymes secretion. Furthermore, CCK was shown to induce satiety by interacting with the vagus nerve sensory fibers and subsequently brain satiety centers [101]. Fasting CCK levels are increased after RYGB surgery [102]. CCK postprandial levels are either not changed or increased, with a more rapid rise after meal ingestion, in RYGB patients [103,104]. These CCK changes are likely due to the anatomical alteration and rapid gastric transit leading to altered postprandial levels and maybe responsible for the increased satiety after RYGB.

Bile acids and weight loss after RYGB

Plasma bile acids (BA) were suggested to affect genes implicated in inflammation, obesity, and glucose metabolism [105]. Serum BA increases gradually in rats, starting at week 14 post RYGB [106]. A twofold increase was also shown in human studies after RYGB, independent of weight loss [107,108]. This increase in serum BA involves both fasting and peak postprandial levels [102]. Alternatively, although fecal BA levels peak in the first days post RYGB in rats, they normalize afterwards with a trend towards lower fecal BAs compared to sham controls [106]. This was also seen in an ileal transposition rat model which alters the small bowel anatomy in a similar fashion to RYGB [109]. These findings were replicated in a small human study by Odstrcil et al in which fecal BA absorption did not increase when measured at 5 and 14 month post RYGB [110]. Following RYGB surgery, the plasma Cholic acid: Chenodeoxycholic acid (CA: CDCA) ratio in obese rats declines to levels observed in lean animals. Decreased ratio of CA to CDCA derived BAs is also seen in stool, suggesting a change in the bile acid pool post-RYGB surgery [106]. The ratio is not significantly different between RYGB and nonobese, weight- and age-matched human controls [102]. Markers of hepatic BA biosynthesis and uptake do not increase after RYGB surgery, suggesting that there is no increased hepatic production or decreased absorption of BAs to explain the rise in serum levels. In contrast, gene expression analysis indicates more BA reabsorption in the biliopancreatic limb of the small intestine, highlighting the importance of enterohepatic recycling to the increased serum BA levels [106,109]. Thus, in conclusion, serums BA are increased after RYGB with improved CA: CDCA ratio.

Intestinal motility after RYGB

There is a paucity of data on intestinal motility after RYGB. Solid food transit in the small bowel seems to be slower after RYGB while colonic motility was similar up to 72 hours [84,111]. Another study used a lactose breath test and showed accelerated orofecal transit which could be due to faster gastric emptying and/or small bowel bacterial overgrowth [81]. As opposed to solids, liquids were shown to empty faster into the cecum. The faster liquid transit may contribute to the early rise in PYY and GLP-1 after RYGB and potentially improve satiety [85]. In summary, after RYGB, liquids small intestinal transit seems to be faster while the opposite holds for solids. This discrepancy between solids and liquids transit may contribute to improved satiety and satiation after RYGB.

Impact of RYGB on the microbiome and relation to weight loss

An expanding literature supports a role for the gut microbiome in obesity and after RYGB weight loss. When obese-lean discordant twin pairs were compared, gut microbiome of the obese group was less diverse [112]. Further, transfer of gut microbiome from lean and obese

subjects can induce metabolic phenotype in germ-free mice [113]. Most of the microbiome-focused studies in RYGB were of small sample size with variable results as summarized in a recent review [114]. Monitoring bacterial genera post-RYGB showed less Firmicutes, such as Lactobacillus, as well as Actinobacteria such as Bifidobacterium decreased after RYGB. Conversely, Bacteroides and Alistipes, of the phylum Bacteroidetes, significantly increased after RYGB [115-117]. Similar gut microbial changes were seen after non-surgical weight loss [112,118]. Unlike in non-surgical weight loss, there was an increased abundance of Proteobacteria, specifically Escherichia coli, after RYGB [115-117,119-123]. Enterobacteriaceae and Pasteurellaceae were also associated with weight loss after RYGB [122,123]. Finally, compared to obese microbiota, RYGB gut microbiota transplant into germ-free mice led to weight loss and improved glucose tolerance [117,124,125]. These findings suggest that RYGB, compared to non-surgical weight loss, produces a specific shift in the gut microbiota which may induce weight loss.

Conclusion

RYGB induced surgical changes lead to significant alterations in neural and gastrointestinal physiology as well as the microbiome. These changes are likely to be collectively responsible for the observed weight loss post RYGB and may guide innovative and viable future weight loss interventions targeting these mechanisms in the future.

Author Contributions

Dr. Hussan was involved in conception, design, review of data, and drafting and critical revision of the manuscript. The above author had full access to all of the data in the study and takes responsibility for the integrity of the data. Drs. Ugbarugba, Krishna, Conwell, Bradley, Clinton and Needleman contributed to the design, interpretation of data, writing of the manuscript, and final review of the manuscript. All gave final approval of the submitted manuscript and take responsibility for the integrity of the work.

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Conflict-of-interest Statement

The authors do not have any relevant conflicts of interest (including relevant financial interests, activities, relationships, and/or affiliations).

Data Sharing Statement

No additional data are available.

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