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The neuroendocrine effects of bariatric surgery on appetite and obesity

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THE NEUROENDOCRINE EFFECTS OF BARIATRIC SURGERY ON APPETITE AND OBESITY

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ABSTRACT

Obesity and adiposity continue to be a concern in the United States and other western developed nations. It effects different populations with inequity, attributing to comorbidities and decreasing quality of life. Despite many different weight management techniques, bariatric surgery has become an effective treatment inducing long term sustained weight loss. These procedures historically have induced weight loss through direct anatomical and physiological changes. More recently, bariatric surgery has been considered an endocrinologically active procedure inducing weight loss through hormonal controls. The two main procedures performed today are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy. Comparing these procedures, RYGB induces greater increases in incretin production than sleeve gastrectomy. Numerous conflicting studies show variable ghrelin changes between pre- and post-procedure conditions for both RYGB and sleeve gastrectomy. These hormonal changes all function within a complex homeostatic energy system associated with adipose tissue, gastrointestinal hormones, and the central nervous system. The lack of understanding surrounding the hormonal controls following bariatric surgery provide areas for future study, important to refining surgical techniques.

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LIST OF ABBREVIATIONS

BMI .... Body Mass Index

CCK .... Cholecystokinin

GHRH .... Growth Hormone Releasing Hormone

GHSR .... Growth Hormone Secretagogue Receptor

GIP .... Gastric Inhibitory Polypeptide

GLP-1 .... Glucagon-Like Peptide 1

GOAT .... Ghrelin O-Acyl Transferase

LABS .... Longitudinal Assessment of Bariatric Surgery

LAGB .... Laparoscopic Adjustable Gastric Banding

NPY .... Neuropeptide Y

NTS .... Solitary Tract Nucleus

PPY .... Polypeptide Y

PVN .... Paraventricular Nucleus

RYGB .... Roux-en-y Gastric Bypass

UCP1 .... Uncoupling Protein 1

WHO .... World Health Organization

INTRODUCTION

Obesity has become a chronic and highly prevalent illness in the United States and other western developed nations ("Obesity: preventing and managing the global epidemic.," 2000). Obesity poses negative consequences upon effected individuals as there is a significant risk of comorbidities attributed to obesity, and also obesity alone can cause a decreased quality of life (Wang et al., 2011). To attempt to manage this epidemic, communities seek to provide resources directed towards the prevention and management of obesity. Public health efforts including increased education, healthy food options, and opportunities for diet and exercise have been somewhat effective at reducing obesity among certain populations (Wolfe et al., 2016). Despite these interventions and known controls, obesity continues to be a problem in the Western world ("Obesity: preventing and managing the global epidemic.," 2000).

Bariatric surgery has become an effective treatment method for individuals struggling with extreme obesity, although specific indications for surgical interventions are evolving rapidly (Wolfe et al., 2016). These surgical techniques were historically established in anticipation of induced weight loss through anatomical and physiological modulation. Though these procedures have evolved over time, they typically utilize a combination of either reducing the capacity of the gastric pouch or diminishing intestinal absorption to induce weight loss (Faria, 2017). Some procedures also use a combination of the two, such as in Roux-en-Y Gastric Bypass (RYGB).

Though these procedures can successfully elicit weight loss through these changes, there are also enteroendocrine signaling factors that are modulated post-procedure (Casimiro et al., 2019). The differences observed among these hormonal factors depend upon the surgical procedure, production and release of the signaling molecule, and can change with time post-procedure (Nannipieri et al., 2013). The changes to enteroendocrine signals post-procedure can also impart a physiological effect upon the comorbidities seen with obesity prior to observed significant weight loss (Kalinowski et al., 2017). Selection of bariatric procedures for different patients has transitioned from being solely about reduction of gastric capacity and inducing malabsorption and instead adapted to become at least partially directed towards inducing enteroendocrine controls of eating behaviors (Lo Menzo et al., 2015). Despite this focus, there are conflicting studies regarding the progression of signals following procedure, which can be misleading (Casimiro et al., 2019). Because of this, comparison of the comprehensive signaling pathways following bariatric surgery may result in better post-surgical outcomes and refinement of specific indications for bariatric surgical procedures.

BACKGROUND

OBESITY

Variations in weight, both acutely and chronically, have long been a concern of healthcare professionals because of the impact that body weight has on an individual's overall health (Middlemiss and McEniery, 2017). Obesity has become an epidemic throughout western, developed nations attributing to increased healthcare costs, decreased life expectancy, and decreased quality of life (Wang et al., 2011). The multifaceted contributors of obesity, both endogenous and exogenous, are potential targets for intervention to prevent and treat obesity as a disease (Rosen, 2014). Because of this, significant resources are dedicated to evaluate these contributing factors, and clarify the mechanism of action for intervention ("Obesity: preventing and managing the global epidemic.," 2000).

Through much of human history, weight gain and fat storage have been associated with signs of prosperity and health ("Obesity: preventing and managing the global epidemic.," 2000; Wells, 2012). This is largely because consumption of food was necessary for surviving the challenges of famine and hard labor ("Obesity: preventing and managing the global epidemic.," 2000). As food availability and standards of living improved, these concerns have changed drastically, creating an “obesogenic environment” (Rosen, 2014). Because of this, public health efforts have increasingly shifted to address the growing threat of overconsumption leading to obesity ("Obesity: preventing and managing the global epidemic.," 2000).

Clinical implications of obesity have been documented dating back to instances in Greco-Roman times, however, little progress was made towards understanding the condition until the 20^{th} Century ("Obesity: preventing and managing the global epidemic.," 2000). During the 1900s, our understanding of the physiology of obesity improved significantly. In 1948, the World Health Organization first recognized obesity as a disease and hosted the first special obesity consultation in 1997 (James, 2008). Within the United States it took until 1998 for the National Institutes of Health to identify obesity a disease, and The American Obesity Society followed suit in 2008 (Rosen, 2014). And even more recently, the American Medical Association recognized obesity as a disease state in 2013 (Rosen, 2014). These changes have magnified focus on obesity as a medical condition, which has driven research towards understanding the physiological processes responsible and interventions necessary to address the concerns of obesity as a major health problem.

Globally, the prevalence of obesity has continued to increase. In 1980, global obesity was recorded at a rate of 28.8% for men and 29.8% for women (Ng et al., 2014). By 2013, the rates had increased to 36.9% of men and 38% of women (Ng et al., 2014). Increases in obesity rates have been more dramatic in children than adults, increasing by 47.1% between 1980 and 2013, while the overall adult population increased by 27.5% during the same time period (Ng et al., 2014).

While population increases of obesity are prevalent globally, specific populations are affected unequally. This inequity can be seen across a variety of factors including age, gender, ethnicity, socioeconomic status, and environment (Bays et al., 2008; Engin, 2017; McLaren, 2007; Ng et al., 2014; Wang and Beydoun, 2007; Wang et al., 2011). Increases in childhood obesity are prevalent among younger aged children in developed countries (Ng et al., 2014). Also, women experience obesity at a higher rate than men (Bays et al., 2008). In 2013, the proportion of adult women who were overweight or obese was 36.9% compared to 28.8% of men (Ng et al., 2014). These differences can be attributed in part to the effects of sex hormones. Androgens are associated with increased visceral adiposity, while estrogens are associated with increased peripheral adiposity (Bays et al., 2008). Individuals in areas of lower socioeconomic status are more likely to be obese than those in areas of higher socioeconomic status in developed nations (McLaren, 2007). In the United States, there is an inverse correlation between socioeconomic status and obesity among Whites but not among African Americans or Hispanics (Wang and Beydoun, 2007). People in urban areas also have a greater rate of obesity than those who live in rural areas (Engin, 2017). While obesity is prevalent at different rates across populations, it continues to be a systemic concern with significant consequences on the global population as a whole. Increasing obesity prevalence globally contribute to these concerns.

Excess body fat mass described in an obese state can be attributed to the pathogenic nature of obesity. This adiposopathy or a “pathologic adipose tissue [inducing] anatomic/functional disturbances” can contribute to multiple comorbidities (Bays, 2011). These comorbidities include metabolic diseases, atherosclerosis, hypertension, dyslipidemia, and type II diabetes mellitus (De Lorenzo et al., 2019). Other chronic conditions associated with increased adiposity include cardiovascular diseases, obstructive sleep apnea syndrome, gallbladder stones, asthma, neurological diseases, polycystic ovary syndrome, nonalcoholic fatty liver disease, gastrointestinal reflux disease, osteoarthritis, and some cancers (De Lorenzo et al., 2019). In addition, obesity is associated with chronic inflammatory state, further exacerbating the disease state (Bays et al., 2008). The early and accurate diagnosis of obesity is essential to addressing its pathology and providing clinical intervention ("Obesity: preventing and managing the global epidemic.," 2000).

Increased adiposity is a function of energy balance, either an excess of caloric intake or insufficient energy expenditure (Hall and Guo, 2017; Walley et al., 2009). Variations in this balance over a sustained period of time can attribute to the development of obesity. Obesity is defined as an abnormal, excessive accumulation of fat in adipose tissue ("Obesity: preventing and managing the global epidemic.," 2000). This accumulation can manifest clinically as increased body weight and hypertrophy of adipose tissue which can attribute to a reduced quality of life and risk of comorbidities (Wang et al., 2011). As discussed previously, there are interventions available to prevent and manage obesity, however diagnosis and detection remain important to the clinical picture (Nimptsch et al., 2019).

To evaluate patients body mass, healthcare professionals use a screening tool to estimate body fat based on height and weight called a Body Mass Index (BMI). This metric can be calculated using the following equation:

$$BMI = Weight\ (kg)/Height^2\ (m^2)$$

The BMI of the individual is used to classify an individual as underweight, normal, overweight, or obese in accordance with the World Health Organization’s guidelines (see Table 1).

Table 1. Classifications of adults according to BMI

Classification of adults according to BMI[a]

Classification	BMI	Risk of comorbidities
Underweight	<18.50	Low (but risk of other clinical problems increased)
Normal range	18.50–24.99	Average
Overweight:	≥25.00	
Preobese	25.00–29.99	Increased
Obese class I	30.00–34.99	Moderate
Obese class II	35.00–39.99	Severe
Obese class III	≥40.00	Very severe

("Obesity: preventing and managing the global epidemic.," 2000)

While BMI is an important screening tool, it does not utilize a direct measurement of adiposity (Kyle et al., 2003). Other factors involved in body weight, which are independent of adiposity, can influence this measurement, such as muscle mass and fluid retention (Nimptsch et al., 2019). Other factors can also influence BMI independent of adiposity including age, lean body mass, and ethnicity (Nimptsch et al., 2019). Therefore, BMI alone cannot be used as diagnostic tool, but is still an important metric for evaluating patient health.

This “Obesity Paradox,” or the classification of different individuals into the same BMI with different clinical and biochemical characteristics, makes it difficult to accurately and precisely provide a complete picture using only BMI (De Lorenzo et al., 2019). Both fat mass and fat free mass can also contribute to a total body mass which is taken into consideration for calculations of BMI, however a large fat mass and a small fat free mass are both independently associated with greater risk of early mortality (Sorensen et al., 2020). This difference can be seen in the lower cutoffs of BMI being used in Non-Hispanic Asian populations to classify obesity, because of the relative risk of mortality and morbidity are higher at an equivalent BMI in this group (Muller et al., 2016; Ogden et al., 2015). When considering risk for certain comorbidities of obesity it remains important to evaluate an entire clinical picture of the individual, not only the predisposition associated with obesity (Segal et al., 1987).

In addition, correlations between body weight, BMI, and the morbidity of certain conditions associated with obesity have been documented (De Lorenzo et al., 2013; Duncan et al., 2009; Keys et al., 1972; Ogden et al., 2015). For example, increased BMI and body weight attribute to metabolic diseases, atherosclerosis, hypertension, dyslipidemia, type II diabetes and the significant list of comorbidities mentioned previously (De Lorenzo et al., 2019). While these comorbidities are not directly associated with BMI, they may be more closely related with other metrics of body composition (Bays et al., 2006; De Lorenzo et al., 2019). These can include measuring waist circumference which is better associated with visceral fat distributions, bioelectrical impedance, dual x-ray absorptiometry, skinfold methods, magnetic resonance imaging and other techniques. Because waist circumference provides a better measure of visceral fat distributions, it may provide a better assessment of metabolic disease attributed to obesity (Bays et al., 2006). These are not metrics have been used in the past and currently to assess obesity and its associated morbidities. However, they are not as common because of invasiveness and availability of technology(De Lorenzo et al., 2019). Despite these challenges, the common use of BMI emphasizes the importance of evaluating the entire clinical profile of patients when assessing their overall health and risk factors associated with obesity instead of BMI alone(Segal et al., 1987).

OBESITY INTERVENTIONS

Multiple models have been proposed to explain weight regulation. Historically, a model which compares energy expenditure to energy intake (also known as the “calories in, calories out” model) has been used (Hall and Guo, 2017). However, this model does not account for variabilities in energy balance and homeostatic signals that are associated with static weight (Hall and Guo, 2017). The regulation of body weight is multifaceted and includes genetic, epigenetic, physiological, behavioral, sociocultural and environmental factors (Bray et al., 2016; "Obesity: preventing and managing the global epidemic.," 2000).

Body weight is remarkably constant and tends to be the result of a balance of intake and energy output, while also being controlled by internal homeostatic control mechanisms (Beaulieu et al., 2018). Weight management interventions can include lifestyle style changes, medications, and surgical interventions (Jensen et al., 2014). The most recognizable of these weight management techniques include implementing diets to control calorie consumption. Caloric restriction, time restrictive eating, restricting certain food types, and other types of limitations have been used with varying results (Jensen et al., 2014; Liu et al., 2022). In addition to diet, adding or increasing exercise activity is another lifestyle change that can be altered to manage chronic obesity (Bays et al., 2006). Other therapies such as pharmacotherapy or surgery are sometimes recommended in addition to these lifestyle changes (Bays et al., 2006). These interventions must be assessed using an individual’s past medical history as a comprehensive consideration of what may be best for them.

Lifestyle Changes to Reduce Obesity

Lifestyle changes are the least invasive of these interventions. For example, lifestyle interventions can achieve loss averages at approximately 10% after 1 year, with maintained weight loss displaying a 5.3% loss over an 8-year span (Wolfe et al., 2016). Lifestyle changes include both diet and physical activity changes, which address both caloric intake and energy expenditure.

Caloric intake restriction is an effective mechanism to assist in modest weight loss (Calbet et al., 2015; Liu et al., 2022; Manchishi et al., 2018; Rynders et al., 2019; Schubel et al., 2018). Specifically, diets that restrict the caloric intake of individuals to less than the energy required for weight maintenance have been shown to be effective at inducing weight loss (Bray et al., 2016). Meal composition can also have an influence on weight loss (Feingold, 2000; Huo et al., 2015). For example, the Mediterranean style diet, characterized by an increased intake of monounsaturated fatty acids, may significantly be associated with a decrease in bodyweight and BMI (Feingold, 2000; Huo et al., 2015). Other beneficial results include reductions in hemoglobin A1C, reductions in fasting plasma glucose, reductions in fasting insulin, and reduced cardiovascular disease risk (Feingold, 2000; Huo et al., 2015). However, there are challenges in achieving weight loss with methods that involve diet changes due to patient compliance, especially for diet changes implemented over long periods of time ("Obesity: preventing and managing the global epidemic.," 2000)

Other diet variations including meal frequency, time restrictive eating, and food preparation behaviors have also been recommended for weight loss (Liu et al., 2022;

Rynders et al., 2019). For example, eating out more frequently is associated with obesity, higher body fat content, and higher BMI. Therefore, reductions in restaurant meals may be targeted for weight loss (Mitchell et al., 2015). There might be other influences related to diet that may induce weight loss such as intake restriction and timing of caloric intake. However, time-restricted eating regimens have not been shown reduce body weight, body fat, or metabolic risk factors more than daily caloric restriction (Liu et al., 2022; Rynders et al., 2019).

Increases in physical activity have been associated with reductions in body weight and BMI, in addition to benefits to health that are independent of weight loss (Bray et al., 2016). The American Diabetes Association and other organizations recommend 150 minutes per week of physical aerobic activity to assist with weight loss ("Obesity: preventing and managing the global epidemic.," 2000). Research studies also suggest that physical activity as an adjunct to weight-reducing diets, might be more effective than diets alone, especially in terms of weight loss and improvements in blood lipids and blood pressure (Schwingshackl et al., 2014). However, issues with the implementation and adherence to physical activity programs often occur (Bray et al., 2016). Weight loss can also occur independently of physical activity changes, however physical activity up to 90 minutes per day may be needed for sustaining that weight loss (Bray et al., 2016; Jakicic et al., 2003; Jakicic et al., 2008; McTiernan et al., 2007).

Medications to Reduce Obesity

In addition to lifestyle changes there are a variety of medications that are approved by the Food and Drug Administration (FDA) for the management of chronic obesity. These medications are typically approved for individuals with a specific BMI range, usually a BMI $\geq$ 27 with a comorbidity (Jensen et al., 2014). It is suggested that the medication be supplemented with comprehensive lifestyle interventions (Jensen et al., 2014). These medications typically work by modifying appetite mechanisms or by inhibiting dietary intake (Ryan, 2022). Medications like naltrexone/bupropion, liraglutide, phentermine/topiramate, and semaglutide all target controls of appetite regulation either inhibiting hunger or promoting satiation (Ryan, 2022). Other medications like orlistat function through blocking the absorption of dietary components like fats, promoting the adherence of low fat meals (Ryan, 2022). There are consequences associated with the use of anti-obesity medications, including side effects and interactions with concomitant medications. Additionally, the cessation of these medications usually results in weight regain (Ryan, 2022). Despite these challenges, these can be an effective treatment of obesity when used in conjunction with lifestyle interventions.

Surgical Methods to Reduce Obesity

Bariatric surgery has become a recommended treatment for individuals with extreme presentations of obesity (Courcoulas et al., 2018; Wolfe et al., 2016). Surgery can be indicated for individuals who have failed to achieve sustained weight loss by non-surgical means (Courcoulas et al., 2018). Criteria for surgery were outlined by the National Institutes of Health consensus panel in 1991 where it was determined that bariatric surgery is appropriate for patients with a BMI > 40 as well as some patients with a BMI between 30-40 with specific comorbidities (Wolfe et al., 2016). It is important to recognize that weight loss in bariatric surgery patients is highly variable with some patients experiencing little to no weight loss (Wolfe et al., 2016). This weight loss typically occurs in the first 12 months post-procedure reaching a nadir, and may be followed by an extended period of modest weight regain over the next 3-5 years (Wolfe et al., 2016). There are also some important safety concerns associated with bariatric surgery. The 30 day follow up for the Longitudinal Assessment of Bariatric Surgery (LABS) consortium reported mortality in 0.3% of all patients, 0.2% following laparoscopic procedures and 2.1% for open gastric bypass (Wolfe et al., 2016). Mortality was also partially predicted by extremes of BMI, obstructive sleep apnea, inability to walk 200 feet, and a history of deep vein thrombosis while other factors may include age, gender, other comorbidities, and smoking (Smith et al., 2011; Wolfe et al., 2016).

There are different types of bariatric surgery with varying levels of invasiveness, gastrointestinal rearrangement, risk to post-surgical complications, and anticipated relative weight loss (Lo Menzo et al., 2015; Wolfe et al., 2016). The purpose of the surgery is to restrict the size of the gastric pouch, reduce the absorptive potential of the digestive tract, or a combination of both (Wolfe et al., 2016). Though these anatomical modifications have been the targets of bariatric surgery, there is evidence that these procedures may have additional effects on neuroendocrine signaling associated with appetite, satiety, energy levels, and physical activity (Lo Menzo et al., 2015; Wolfe et al., 2016). These changes include variable reductions in ghrelin, and increases in peptide YY (PYY) (see Table 2) (Lo Menzo et al., 2015). Some of these effects have been attributed to nutritional bypass of the upper intestinal tract which reduces the absorptive capacity of the small intestine and quicker delivery of nutrients to the distal portions of the intestinal tract, resulting in quicker nutritional feedback (Lo Menzo et al., 2015; Rubino and Gagner, 2002).

Table 2. Common enetero-hormonal changes after bariatric surgery

Common entero-hormonal changes after bariatric surgery.

	Origin	Satiety	Glycemic control	GI motility	RYGB	LSG	LAGB	BPD	BPD-DS
GLP-1	L-cells	↑	↑	↓	↑	↑	No Δ	↑	↑
GIP	K-cells	No Δ	↑	No Δ	↓	?	No Δ	↓	↓
PYY	L-cells	↑	↑ or No Δ	↓	↑	↑ or NoΔ	No Δ	↑	↑
Ghrelin	Oxyntic	↓	No Δ	No Δ	↓	↓↓	No Δ	No Δ	↓↓

GLP-1: glucagon-like peptide 1; GIP: glucagon and gastric inhibitory polypeptide; PYY: peptide YY; RYGB: Roux-en-Y gastric bypass; LSG: laparoscopic sleeve gastrectomy; LAGB: laparoscopic adjustable gastric banding; BPD-DS: biliopancreatic diversion with duodenal switch.

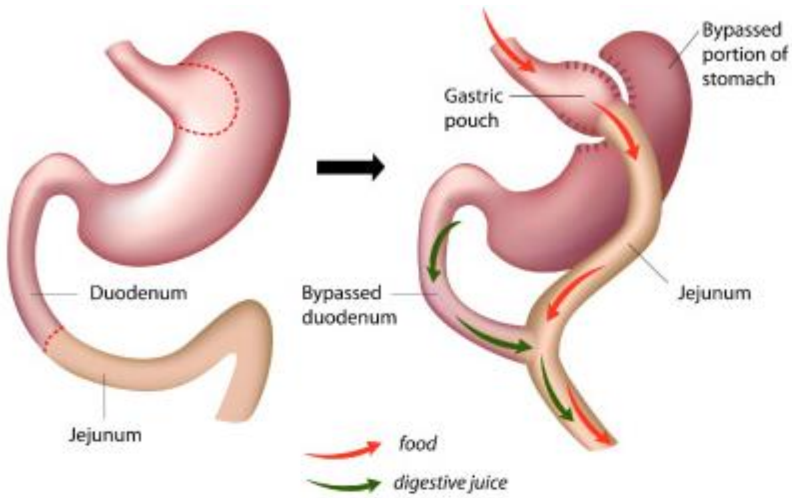
(Lo Menzo et al., 2015)

There are multiple bariatric surgery procedures that are performed today including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, biliopancreatic diversion with a duodenal switch, and the implantation of different devices (Wolfe et al., 2016). Among the implantable devices for bariatric surgery, laparoscopic adjustable gastric banding

(LAGB) and intragastric balloon procedures are very similar as they reduce the size of the gastric pouch. LAGB procedures place an adjustable band below the esophagogastric junction which allows for the creation of a smaller gastric pouch (Lo Menzo et al., 2015). Gastrointestinal balloons are endoscopically placed within the stomach and functionally reduce the internal size of the stomach. RYGB has become a much more popular procedure than LAGB because it shows a greater relative weight loss (Golzarand et al., 2017).

The RYGB surgical process is more complex as illustrated in Figure 1. RYGB reduces the size of the gastric pouch to approximately 15-30 cm^3 by dividing the proximal and distal potions of the stomach along the lesser curvature of the stomach. This is done because the fundus of the stomach is more elastic, and by eliminating this area surgeons are able to more effectively reduce the gastric pouch capacity. Following this, the jejunum is then separated 40-60 cm from the ligament of Treiz. The jejunum is anastomosed in a “Y” formation with a jejunojejunostomy 100 to 200 cm from the original division bypassing a portion of the stomach, duodenum, and part of the jejunum. The Roux limb of the jejunum is then attached to the smaller proximal gastric pouch creating gastrointestinal continuity. The bypassed portion of the stomach, jejunum, and the length of the Roux limb is variable to determine malabsorption in this procedure (Wittgrove et al., 1994).

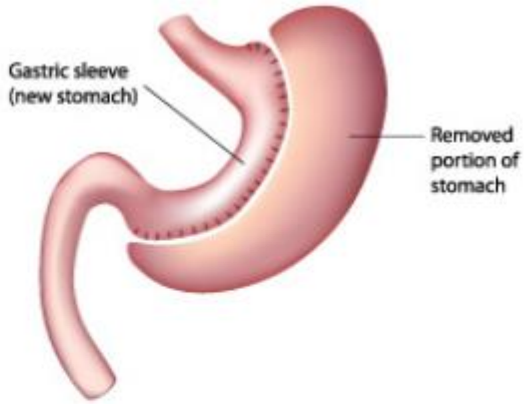
Figure 1. Illustration of Roux-en-Y Gastric Bypass (RYGB)



("Roux-en-Y Gastric Bypass (RNY)," 2023)

Finally, sleeve gastrectomy resects approximately 80% of the stomach creating a tubular shaped stomach following the lesser curvature of the fundus (Wolfe et al., 2016). There is no gastrointestinal anastomosis required for this procedure. While there is some restriction on food intake with a smaller gastric pouch, gastric emptying is also accelerated following this procedure (Wolfe et al., 2016). A biliopancreatic diversion with a duodenal switch is similar to a sleeve gastrectomy in regards to reduction of the gastric pouch, however, an anastomosis of the proximal duodenum and bypassed intestine must be performed. The biliopancreatic diversion with duodenal switch has been performed infrequently because of the greater incidence of short- and long-term complications (Wolfe et al., 2016).

Figure 2. Sleeve Gastrectomy



("Vertical Sleeve Gastrectomy," 2023)

While it is apparent that there are procedural differences between these bariatric procedures, there are also physiological differences. Each method contributes to weight loss when adjunctly used with lifestyle intervention. There are disparities in the outcomes between procedures as well. For example, greater weight loss and weight loss maintenance is seen among patients that receive RYGB compared to LAGB (Courcoulas et al., 2018). RYGB takes advantage of the malabsorptive aspects of the bypassed small intestine not engaging in absorption of dietary intake. In addition to restricting the size of the gastric pouch, unlike LAGB or sleeve gastrectomy which only reduce the size of the gastric pouch (Akkary, 2012). Some weight regain can be observed following the initial weight loss achieved in both LAGB and RYGB procedures. Overall, approximately 75% of RYGB participants maintain at least 20% weight loss and 50% of LAGB participants maintain at least 16% weight loss over a period of 7 years (Courcoulas et al., 2018). Many LAGB patients have their procedures reversed or converted into a RYGB to induce greater weight reduction or correct complications seen with LAGB such as band slippage or a distended gastric pouch (Mognol et al., 2004). Sleeve gastrectomy also led to an average excess weight loss of 47% after 7 years compared to 55% mean excess weight loss with RYGB, however, this difference was not clinically significant (Gronroos et al., 2021).

Post-procedural adverse events have been associated with bariatric surgery. However, bariatric procedures compare favorably to other commonly performed surgical procedures that include coronary bypass graft, arthroplasty, cholecystectomy, and hysterectomy (Longitudinal Assessment of Bariatric Surgery et al., 2009; Wolfe et al., 2016). Surgical complications can also occur, but the incidence rate is low (Wolfe et al., 2016). Following bariatric surgery, some patients can experience worsening of gastroesophageal reflux disease symptoms after sleeve gastrectomy and RYGB (Peterli et al., 2018). Other mid- and longer-term complications include intestinal obstruction, marginal ulcer, ventral hernia, gallstones, nephrolithiasis, hypoglycemia, mineral and vitamin deficiency, and weight regain (Wolfe et al., 2016). LAGB can result in complications related to the band including gastric band slippage, which occurs at a rate of approximately 2% per year (Wolfe et al., 2016). The malabsorptive effects caused by RYGB and biliopancreatic diversion with duodenal switch have also raised some concerns (Lo Menzo et al., 2015; Wolfe et al., 2016).

Reduction of obesity related comorbidities following bariatric weight loss can occur quickly after surgery (Pi-Sunyer, 2009). For example, remission of type 2 diabetes can begin before there is significant weight loss and after the immediate effect of postoperative starvation on the blood glucose level has dissipated (Buchwald et al., 2009). However, there are differences between the various bariatric surgical procedures in reducing the manifestations of diabetes. Following RYGB, some patients required a lower number of antidiabetic medications when compared to sleeve gastrectomy to maintain a primary end point of hemoglobin A_{1C} (Peterli et al., 2018). Currently, it remains unclear why different diabetic outcomes occur between these procedures. Therefore, additional research is necessary to evaluate the effects of the surgical procedures on diabetic patients.

ADIPOSE TISSUE

Obesity by definition is “a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired” ("Obesity: preventing and managing the global epidemic.," 2000). Adipocytes, the parenchymal cells associated with adipose tissue, play a significant role in storing excess energy as fat, endocrine communication, and insulin sensitivity (Goossens, 2017; Richard et al., 2000). The mechanisms adipocytes use to retain energy are important factors in understanding obesity.

There are four major types of adipocytes, white, brown, beige, and pink. Each have slightly different variations in function and are characterized by their primary ability to store lipids (Richard et al., 2000). Adipose cells develop from the differentiation of precursor cells, but can also transdifferentiate into the four different types of adipocytes discussed previously (Richard et al., 2000; Stenkula and Erlanson-Albertsson, 2018). Adipose tissue is also heterogeneous, containing multiple cell types including mature adipocytes, fibroblasts, endothelial cells, preadipocytes and macrophages. Overall, adipocytes represent 90% of adipose tissue volume, but less than half of the cellular content (Corvera, 2021; Trayhurn et al., 2006).

White adipocytes make up the largest quantity of adipose tissue by volume in adults(Richard et al., 2000). White adipose tissue can be differentiated visually by its white or yellowish white color and expand to a size of 100 μm when engorged with lipids (Cinti, 2012; Richard et al., 2000). These cells are usually distributed in the subcutaneous and visceral regions of the body, areas that typically store large amounts of lipids

(Corvera, 2021; Trayhurn et al., 2006). The location of white adipocytes helps to differentiate their role and functionality as there are specific regional differences. This differentiation can be influenced by differences in the innervating blood supply, such as the portal system in the gastrointestinal tract and adjacency to other tissues. Because of the dependence upon other cell types, white adipose tissue is also fairly heterogeneous containing multiple cell types including mature adipocytes, fibroblasts, endothelial cells, preadipocytes and macrophages. It is notable that adipocytes may make up less than half of the cells within this adipose tissue (Corvera, 2021; Trayhurn et al., 2006).

Although adipocytes may make up less than half the cells in this tissue presentation, they are the parenchymal cells of white adipose tissue (Trayhurn et al., 2006). White adipocytes contain a large central lipid droplet that pushes other organelles including the nucleus to the cell's periphery (Richard et al., 2000). The storage of triacylglycerols in this liposome allows white adipocytes to expand to nearly 100 μm in diameter contributing to up to 90% of the cell's volume (Cinti, 2012; Thompson et al., 2010). Because of their relative volume and ability to undergo expansion during lipid accumulation, they are central to obesity physiology and pathology (Cinti, 2012; Corvera, 2021; Thompson et al., 2010; Trayhurn et al., 2006).

Brown adipocytes differ from white adipocytes in ways that help facilitate their unique function. Brown adipocytes range from 15-50 μm in diameter and contain a different organization of internal structures (Sarjeant and Stephens, 2012). They have an increased number of mitochondria compared to white adipocytes and many multilocular lipid droplets within an ellipsoid cell (Cinti, 2005). The nucleus of these cells is more centralized compared to the peripheral location within white adipocytes, and the entire cell shape is more ellipsoid (Richard et al., 2000; Sarjeant and Stephens, 2012). Brown adipose tissue is also visually browner in color as a reflection of an increased number of mitochondria present in these cells.

Besides containing additional mitochondria, the mitochondria of brown adipocytes are also unique. Specifically, the mitochondria express uncoupling protein 1 (UCP1). UCP1 expression allows for non-shivering thermogenesis to occur (Cinti, 2012). In addition, proton gradients across the inner mitochondrial membrane can be reduced without the production of ATP (Richard et al., 2000). Because ATP is not phosphorylated, the reduction of the proton gradient releases potential energy without providing ATP for cellular function.

The distribution of brown adipose tissue changes with age and behaviors. In mammals, brown adipose tissue is more prevalent during infancy and, for some species, during hibernation. In human adults, brown fat is primarily located in visceral deposits adjacent to the aorta (Cinti, 2012). Notably, transdifferentiation of pre-adipocytes and other mature adipocytes into brown adipocytes can occur in response to specific conditions including cold exposure, increased norepinephrine, and activation or inhibition of a number of receptors (Cinti, 2012; Richard et al., 2000).

Beige adipocytes, also known as paucilocular adipocytes, are often present in the same locations as white adipocytes, but they display a cellular anatomy intermediate to white and brown adipocytes (Cinti, 2012). Beige adipocytes develop through transdifferentiation in response to cold exposure, exercise, pre- and post-biotics, pharmaceutical agents, plant-based bioactives, or selective adipokines (Richard et al., 2000). They develop within subcutaneous white adipose tissue, and may help protect against obesity and the associated comorbidities (Richard et al., 2000).

Finally, pink adipocytes are a special type of adipocytes specific to subcutaneous white adipose tissue during the end of maternal pregnancy, and persisting through lactation (Cinti, 2018). These adipocytes assist in lactation, displaying epithelial-like structures including compartmentalized lipid droplets, cytoplasmic projections, and abundant organelles (Richard et al., 2000). They assist in the formation of milk-secreting alveoli and transdifferentiate into other types of adipose tissue after lactation has ceased (Cinti, 2018).

The ability of adipocytes to transdifferentiate is an important target for obesity interventions, specifically for the potential of increasing levels of brown fat (Richard et al., 2000). White adipose tissue, because of its relative volume in an obese state, poses the largest physiological contribution to the disease state of obesity. In addition, increases in brown adipose tissue may help to reduce triacylglycerol storage through the uncoupling of ATP production within the mitochondria of these cells(Richard et al., 2000).

Adipose Tissue Distribution

The location of adipose tissue deposits influence the display of various adipocyte functions including differences in lipolysis, adipogenesis, lipogenesis, the expression of adipocyte receptors, and variations in the endocrine and immune processes which contribute to metabolic disease (Bays, 2011). There are two major locations in the body which harbor white adipose tissue. These are classified into either visceral or subcutaneous regions (Bays et al., 2006; Bays et al., 2008; Lewis et al., 2002). Visceral fat sequestered in the intraperitoneal, extraperitoneal, and intrapelvic regions composes approximately 20% of all total body fat in men and 6% in women, while subcutaneous fat can compose up to 80% in men and 94% in women respectively (Bays et al., 2006; Bays et al., 2008; Lewis et al., 2002). Historically, these fat deposits have been considered largely identical with the exception of the anatomical location, however there are heterogeneous differences between the two locations in terms of protein production, and intercellular signaling.

Visceral fat displays differences in protein production for endocrine and paracrine signaling when compared to subcutaneous fat (Arner, 2001). Factors like angiotensinogen, acylation-stimulating protein, and leptin are all produced at a lower rate in visceral tissue compared to subcutaneous, as identified by their mRNA transcription (Arner, 2001). Leptin induces a satiating effect through neural communication, angiotensinogen regulates blood pressure through renal activity, and acylation-stimulating protein has a potent anabolic effect on human adipose tissue (Arner, 2001; Cianflone et al., 1999). The consequences associated with relative production of these factors indicates that visceral fat has a lesser control of global energy balance when compared to subcutaneous fat. Additionally, the relative mass of these two distributions prevents visceral fat from affecting a significant amount of control over adiposity through extracellular signaling (Arner, 2001).

Visceral fat's adjacency to the portal vein, which supplies approximately 80% of all blood supply to the liver, allows it to release the majority of free fatty acids and glycerol to the liver via lipolysis (Bergman et al., 2006; Lewis et al., 2002). This also means that visceral fat when releasing free fatty acids and glycerol releases these to the liver increasing hepatic triglyceride and glucose production. These increases are associated with dysmetabolism and in turn excessive fat related metabolic diseases including hyperglycemia, dyslipidemia, insulin resistance and type 2 diabetes mellitus (Bays et al., 2006). Visceral fat has also been described as having the highest level of metabolic activity, specifically acting through high basal lipolysis, increased sensitivity to catecholamines, and decreased sensitivity to insulin (Bays et al., 2006). These functions as well as the inflammatory activity displayed by adipose tissue are all amplified by visceral fat hypertrophy, which may lead to increased metabolic disease (Bays et al., 2006).

Periorgan fat can be considered a subdivision of visceral adipose tissue. These deposits surround internal organs such as the heart, musculature, vasculature, orbits, and bones imparting direct effects upon those organs it surrounds. In addition to offering physical protection where adipose tissue can serve as padding, this distribution typically presents effects though metabolic activities including lipolysis and the release of inflammatory factors. For example, pericardial and perivascular accumulations can promote congestive heart disease and peripheral vascular disease (Bays et al., 2008). There is also evidence that perivascular adipose tissue can contribute to atherosclerosis due to an “outside to inside” vascular atherogenic model (Bays et al., 2008).

Subcutaneous fat, also known as peripheral fat, acts differently than visceral fat as a result of this heterogeneity. Composing approximately 80% of total body fat in adult males, this distribution of adipose tissue is the largest by volume (Bays et al., 2006). It is sequestered in truncal, gluteofemoral, mammary, and inguinal regions, and as the name subcutaneous implies, this fat resides under the skin. It is described as having the lowest level of metabolic activity when compared to adipose tissue in other distributions (Bays et al., 2008). Because of this, subcutaneous fat may even be considered “protective” (Bays et al., 2008). This heterogeneity in metabolic activity is likely due in part to the predetermination of gene expression, presentation of various cellular receptors, and differences in enzymatic metabolic processes (Bays et al., 2006). It is also important to recognize some regional abdominal distributions of subcutaneous adipocytes display a metabolic function that is between that of subcutaneous fat and visceral fat (Bays et al., 2006). The net release of free fatty acids in a fasting state is greater from visceral adipose tissue when compared to subcutaneous tissue as a result of lipolytic activity (Bays et al., 2006).

Subcutaneous fat displays a greater differentiation of preadipocytes than visceral fat, indicating it has a greater capacity for hyperplasia (Bays et al., 2006). Because of this, it has a higher capacity for anabolic fatty acid uptake, and can serve as a larger reservoir for free fatty acids (Goossens, 2017). This is, in part, because of its higher affinity for binding anabolic regulators like acylation stimulating protein, which promotes triacylglyeride accumulation (Cianflone et al., 1999). As subcutaneous tissue has a greater affinity to differentiate, increasing the total number of cells, it is sometimes called “healthy fat” (Bays et al., 2006).

Overall, the differences in distribution of adipose tissue can be summarized as follows: subcutaneous tissue provides a more stable harbor of triacyl glycerides compared to that of visceral fat. Visceral fat’s adjacency to the portal vein and susceptibility to lipoprotein lipase controls allows it to be more metabolically active becoming a larger contributor to the negative metabolic effects associated with obesity (Bergman et al., 2006; Stenkula and Erlanson-Albertsson, 2018).

Adipose Physiology

Adipocytes, being the parenchymal cells of adipose tissue, have specific functions associated with obesity (Cinti, 2012). One of adipocytes main functions is to facilitate the capture and release of lipids through specialized cellular mechanisms to facilitate a steady state during the times between food intake (Bays, 2011). When dietary intake exceeds energy expenditure for an extended period of time adipocyte's function can become overwhelmed leading to an impaired capacity to accumulate additional lipids (Bays, 2011). Adipocytes and adipose tissue can store a relatively large amount of energy in a dense configuration, however, proper controls are essential to prevent pathogenesis of this adipose tissue as seen in an obese state (Bays, 2011).

Dietary lipid uptake occurs following the consumption of fatty foods. In the lumen of the small intestine, digestion is facilitated by bile salts released by the liver which help to emulsify these lipids. The emulsification process converts these lipids, usually consumed as triacylglycerols into monoacylglycerols. These monoacylglycerol droplets are then taken up by enterocytes where they are converted into triacylglycerols and packaged into chylomicrons (Alves-Bezerra and Cohen, 2017).

In addition to lipid intake, excess dietary consumption of other macronutrients can also contribute to storage of energy as fats (Alves-Bezerra and Cohen, 2017; Liu et al., 2022; Wang and Beydoun, 2007). Hepatocytes have the ability to synthesize lipids through de novo lipogenic pathways. For example, excess intake of large quantities of carbohydrates can be metabolized into acetyl-CoA which can be further modified into palmitate. Palmitate production is limited by the enzyme fatty acid synthase but it can then be modified by desaturases and elongases to create diverse fatty acids for use in triacylglycerol synthesis or elsewhere in other metabolic pathways (Alves-Bezerra and Cohen, 2017). These triacylglycerols, whether derived from de novo or dietary sources, are then typically packaged into lipoproteins to be delivered to tissues.

Chylomicrons and other lipoproteins circulate in the body. These entities contain triacylglycerols and cholesterols bound in a protein shell. Lipoprotein lipase allows for the triacylglycerols within these lipoproteins to be released as glycerol and fatty acids (Thompson et al., 2010). Lipoprotein lipase is a major control in the release of fatty acids from lipoproteins. This process of releasing fatty acids by lipolysis occurs during both feeding and fasting behaviors(Thompson et al., 2010). The facilitating enzyme is released by tissues like muscle that can uptake fatty acids for further metabolic function. It is also released in adipose tissue to facilitate storage. Furthermore, the enzyme also plays a role in dyslipidemia associated with obesity as it varies relative to adiposity(Thompson et al., 2010).

Fatty acids can be transferred through the blood stream via two major mechanisms either within lipoproteins as triacylglycerols or bound by albumin as free fatty acids. This is accomplished through a balance between release of fatty acids into the blood stream via intravascular lipolysis of lipoproteins and lipolysis of adipose tissue triglyceride stores, as well as uptake which is predominantly oxidation in energy expending tissues and re-esterification in adipose tissue (Lewis et al., 2002). There is a small percentage of unbound fatty acids (Thompson et al., 2010). Unbound fatty acids can be taken up by energy deficient cells and are either metabolized through glycolysis and beta oxidation for the formation of energy or stored. It is currently unclear if fatty acid uptake is a diffusion mediated or protein mediated process (Thompson et al., 2010).

A portion of the fatty acids released into circulation can be taken up by adipocytes. Storage within adipocytes engages with lipogenic pathways reforming triacylglycerols from the fatty acid and glycerol molecules delivered across the cell membrane. The esterification of glycerol makes the molecule nonpolar which prevents its translocation across the cell membrane. The continual accumulation of triacylglycerols into the liposome of adipocytes is what attributes to hypertrophy, while also promoting the differentiation of precursor cells into mature adipocytes (Bays et al., 2008).

The accumulation of lipids in the setting of continued positive caloric intake results in the expansion of the adipose tissue organ. This can occur both through the hypertrophy of adipocytes or through the differentiation and proliferation of new adipocytes to facilitate additional storage (Bays et al., 2008). The determination of whether adipocytes respond to a positive caloric benefit through hypertrophy or hyperplasia is dependent upon genetic predisposition and a multitude of regulatory factors (Bays et al., 2008; Sarjeant and Stephens, 2012). The factors that help regulate adipogenesis via proliferation and differentiation include catecholamines, hormones, lipoproteins, lipids, and proteins (Bays et al., 2008; Smas and Sul, 1995). Hypertrophy of adipocytes is more closely associated with metabolic disease such as cardiovascular disease and type 2 diabetes, therefore dysfunction to adipogenesis can contribute to the presentation of these comorbidities (Bays et al., 2008). This discrepancy in how fat is stored helps to explain why some individuals who are obese display excess fat related metabolic disease while others do not, or why some non-obese individuals exhibit excess fat related metabolic disease (Bays et al., 2008).

Hypertrophy of adipocytes occurs in the absence of adipocyte proliferation, and may in some instances be viewed as the failure of adipocytes to proliferate (Bays et al., 2008; Gregoire et al., 1998). Excess cell enlargement is a more potent contributor to metabolic and immune abnormalities when compared to excess adiposity through adipocyte hyperplasia (Bays et al., 2008). Excessive adipocyte hypertrophy can reach a point where further free fatty acid influx is inadequate because there is a resistance or inability to store additional triglycerides. These free fatty acids can become lipotoxic to peripheral tissues and promote metabolic diseases (Bays et al., 2006).

Adipocyte differentiation occurs in the presence of excess caloric balance leading to the accumulation of triacylglycerol while simultaneously being promoted by extracellular factors (Gregoire et al., 1998). Adipocytes will preferentially increase in number or in volume based upon their regional location (Stenkula and Erlanson-Albertsson, 2018). Visceral fat has a greater predisposition for adipocyte hypertrophy compared to the hyperplasia seen in subcutaneous adipocyte stores (Stenkula and Erlanson-Albertsson, 2018).

In addition to fatty acid capture, adipocytes also facilitate the release of fatty acids in times of fasting to serve as an energy source for peripheral tissues (Bays et al., 2006; Thompson et al., 2010). The release of fatty acids is associated with a circulating energy deficiency and is facilitated by a variety of endocrine signals and their effect upon lipases (Bays et al., 2006; Thompson et al., 2010). Hormone sensitive lipase is considered the principal regulator of lipolysis within adipose tissue and the rate-limiting step for the release of free fatty acids (Bays et al., 2006; Thompson et al., 2010). There are also enzymes, desnutrin and monoacylglycerol lipase, which are essential in the metabolic release of fatty acids from triacylglycerols (Thompson et al., 2010). The action of these enzymes facilitate the hydrolysis of triacylglycerols to glycerol and free fatty acids which can then be translocated out of adipocytes and circulated to meet the metabolic needs of energy deficient tissues (Thompson et al., 2010). Some individuals with excess adiposity, can have a reduced expression of hormone sensitive lipase (Langin, 2006). Though it has been recently debated whether hormone sensitive lipase is the limiting factor controlling lipolysis, or if it is other lipases such as desnutrin (Langin, 2006). It is important to recognize during times of fatty acid uptake by adipocytes, release pathways are typically suppressed or inactive (Langin, 2006).

There are endocrine and paracrine regulators that affect the function of hormone sensitive lipase and desnutrin (Langin, 2006). These activators include catecholamines which act on beta-adrenoceptors, and natriuretic peptides which usually function through monophosphates interaction with kinases to phosphorylate and activate hormone sensitive lipase (Langin, 2006). When released these molecules signal an energy deficient state and induce lipolysis (Langin, 2006). The lipolytic effects allow for the release of free fatty acids for use in beta oxidation. Conversely, there are a number of inhibitory pathways that prevent the release of fatty acids (Langin, 2006).

In times of reduced energy intake adipose tissue can also release fatty acids to fuel different tissues (Langin, 2006). Lipolysis is the catabolic process where triacylglycerol is broken down into free fatty acids and glycerol, and typically occurs in the cytoplasm of adipocytes. Fatty acids are then released into the plasma where they can be distributed via circulation to different tissues, such as skeletal muscle. Release of fatty acids from adipose tissue is largely controlled by endocrine pathways including those stimulated by catecholamines and natriuretic peptides (Langin, 2006).

Energy balance facilitated by the mechanisms described previously is necessary to supply tissues with energy and create a homeostatic state. This is facilitated by various adipose released hormonal controls, interacting with other peripheral effectors and the central mechanisms integrated within the hypothalamus (Ahima et al., 1999; Miller et al., 2014). Disruptions to the function of healthy adipose tissue attribute to an obese state, correlating with downstream effectors and the comorbid consequences of obesity (Bays, 2011).

Neuroendocrine Effects on Appetite and Obesity

The body utilizes internal hormonal and neurological controls to balance the intake and output of energy within the system (Hall and Guo, 2017). These signals originate from both central and peripheral tissues creating a comprehensive system for energy homeostasis. This set point is not constant as body weight does fluctuate over time, but instead provides some consistency to body weight in the light of environmental and internal factors (Munzberg et al., 2016). While intake may vary through feelings of satiety, hunger, and hedonic eating behaviors, energy expenditure can also be modulated to reflect some changes in energy intake to maintain close to the established homeostatic set point (Beaulieu et al., 2018). The homeostatic model of energy balance is built upon theories that both energy intake and expenditure are driven by internal signals that are integrated to maintain the homeostatic set point (Shin et al., 2009; Wells, 2012). However, there are extrinsic drivers of energy intake and expenditure that are not the direct result of homeostatic mechanisms (Shin et al., 2009; Wells, 2012).

Intake controls act on two factors: meal initiation and meal cessation (Valassi et al., 2008). Circulating neuroendocrine factors from the alimentary canal induce a satiating feeling following consumption of food, with a notable exception of ghrelin and a few other orexigenic factors (Kojima et al., 1999; Valassi et al., 2008). While this is a simplification of the mechanism that controls body weight regulation, there is a consensus that this system is comprised of three basic components, “(1) a nutrient sensing system providing feedback for the regulated parameters, (2) an integrator making sense of all the internal signals in a given environment, and (3) behavioral, autonomic, and endocrine effector pathways leading to changes in energy intake, efficiency, and expenditure" (Shin et al., 2009).

Meal onset is one point where energy intake is controlled leading to the initiation of the consumption of food. Historically, meal initiation had been considered driven by inter-meal times of reduced blood glucose (Woods, 2004). This theory suggested that the lateral hypothalamic area would recognize times of low blood glucose, inducing a hunger state while the ventromedial hypothalamus would recognize times of high blood glucose inducing a satiated feeling (Valassi et al., 2008). The integration of these two regions would then result in a hunger feeling if blood glucose was low. In contrast, some research has suggested that meal initiation is largely controlled by social, cultural, lifestyle, and related environmental factors (Valassi et al., 2008; Woods, 2004). Only during times of extreme energy deprivation does meal onset appear to be biochemically activated (Valassi et al., 2008; Woods, 2004).

Because meal initiation is mostly controlled by the factors described previously, it is not very easy to modulate these internal or ingrained external factors. Conversely, satiety is more regulated with internal signaling, inducing changes in meal size and ultimately cessation of eating (Woods, 2004). The gastrointestinal system is a single organ system which generates satiety signals during consumption of a meal to regulate food intake on a meal-to-meal basis. These satiety signals include mechano- and chemo-receptors along the alimentary canal which send afferent information to the brain through sensory nerves, and endocrine signaling (Berthoud, 2008; Shin et al., 2009). Additionally, there are autonomic controls of gastrointestinal function modulated by these signals inducing changes in eating behavior (Asakawa et al., 2003).

Along the alimentary canal, the signals responsible for appetite control and energy status are produced in response to food intake, or lack thereof (Chaudhri et al., 2006). The majority of gut hormones alter food intake through eliciting a sensation of fullness therefore reducing food intake and limiting meal size, with the notable exception being the hormone ghrelin (Chaudhri et al., 2006). The most studied energy intake influencing hormones include cholecystokinin (CCK), pancreatic polypeptide, PYY, oxyntomodulin, glucagon like peptide-1 (GLP-1), and ghrelin (Chaudhri et al., 2006). While there are additional hormones, these are of note because they are modulated following bariatric surgery (Chaudhri et al., 2006).

CCK, produced in the I-cells of the duodenum, and jejunum, is released in response to meals with high content of fats and proteins (Buffa et al., 1976; Liddle et al., 1985). Circulating plasma CCK levels reach a maximum approximately 30 minutes after feeding (Chaudhri et al., 2006). Additionally, glucose can cause a significant but smaller elevation in plasma CCK levels (Liddle et al., 1985). CCK is a peptide hormone released postprandially which induces effects including reduced food intake, contraction of the gallbladder, relaxation of the sphincter of Oddi, stimulation of somatostatin release, delays in gastric emptying, inhibition of gastric acid secretion, and reduction of pancreatic enzyme secretion (Chaudhri et al., 2006; Liddle et al., 1985).

Exogenous CCK administered in rats and humans reduces food intake without affecting water intake (Gibbs et al., 1973; Kissileff et al., 1981). However, the effect of these administrations are short lived and are not effective when administered 30 minutes prior to the start of a meal (Gibbs et al., 1973; Kissileff et al., 1981). This meal reducing effect may be in response to reduced gastric emptying seen with exogenous administration (Gibbs et al., 1973; Kissileff et al., 1981). CCK binds to CCK-1R receptors along the vagal sensory terminals delivering a signal to the solitary tract nucleus (NTS) which conveys a sense of fullness, and satiety thereby reducing meal size (Valassi et al., 2008). Intravenous administration of exogenous CCK can significantly reduce the size of a single-food test meal and post-prandial hunger (Valassi et al., 2008). Additionally, antagonists of the CCK-1R inhibit the satiating effects of an intraduodenal administration of fat emulsions (Valassi et al., 2008).

It is unclear how CCK alters food intake, though there are a few different disputed theories (Chaudhri et al., 2006; Moran and McHugh, 1982). CCK may induce an inhibitory effect on appetite through the reduction of gastric motility and the inhibition of gastric emptying as seen when low doses of CCK reduced food intake in rhesus monkeys only after a gastric preload of saline (Chaudhri et al., 2006; Moran and McHugh, 1982). Other theories suggest the action of CCK through pathways independent of the stomach, but rather through vagal afferent fibers (Chaudhri et al., 2006). This is specific to CCK-1 receptors located on the afferent fibers of the vagus nerve, brainstem, and dorsomedial nucleus of the hypothalamus (Chaudhri et al., 2006). Creating lesions in the vagus nerve abolishes the effects of CCK at lower doses of the dose response curve (Chaudhri et al., 2006; Moran and Kinzig, 2004). Overall, research suggests that CCK provides at least some influence on the post-prandial satiety in response to the consumption of food (Chaudhri et al., 2006).

In healthy individuals, pancreatic polypeptide is released primarily by cells at the periphery of the pancreatic islets, but also by the exocrine pancreas and distal gut (Chaudhri et al., 2006; Track et al., 1980). Food intake is the main stimulus for secretion of pancreatic polypeptide, which is proportional to caloric intake (Chaudhri et al., 2006). There is also circadian release that is lesser than that stimulated by caloric intake with a peak at 21:00 hours and a nadir at 02:00 hours (Track et al., 1980).

There are a few different effects facilitated by pancreatic polypeptides. When administered into the brain, pancreatic family peptides including pancreatic polypeptide, neuropeptide Y (NPY), and PYY decrease food intake (Asakawa et al., 2003). Anorexigenic effects associated with pancreatic polypeptide may be the result of hypothalamic integration in the ventral tegmental area. Peripheral effects include delayed gastric emptying and also direct vagal innervation translated towards hypothalamic structures (Chaudhri et al., 2006).

In obese individuals, pancreatic polypeptide secretion and plasma levels are reduced; while in patients with anorexia nervosa these levels are increased (Asakawa et al., 2003). Additionally, pancreatic polypeptide can increase oxygen consumption when administered to mice supporting a role for increased energy expenditure attributing to weight loss (Asakawa et al., 2003). Peripheral administration of pancreatic polypeptide did not induce an inhibitory effect on eating when mice had received truncal vagotomy (Asakawa et al., 2003). This suggests that pancreatic polypeptide binds to receptors on the vagus nerve, and more specifically the dorsal vagal complex. Because of this, pancreatic polypeptide may interact directly with the dorsal vagal neurons and regulate gastric motility and acid secretion (Asakawa et al., 2003)

Pancreatic polypeptide has also demonstrated effects on other appetite control molecules. For example, peripheral administration of pancreatic polypeptide decreases the expression of leptin production in adipose tissue, reducing mRNA production by 74% in food deprived mice, while there is no significant effect on non-food-deprived mice (Asakawa et al., 2003). Mice with an overexpression of pancreatic polypeptide showed a decreased expression of gastric ghrelin and hypothalamic orexin during fasting (Asakawa et al., 2003). More importantly, PYY also has an effect in humans eliciting an anorexigenic response.

PYY is mainly secreted by the L-cells of the distal gut in amounts correlated with ingested calories (Valassi et al., 2008). Exogenous administration of PYY can reduce food intake and extend the interval between meals in animal models (Valassi et al., 2008). Deficiency of PYY has been documented in obese individuals, however peripheral infusion of PYY mimicking average postprandial concentrations can significantly reduce caloric intake. This hormone acts through the vagal afferent pathways directed towards the NTS, and potentially mediated through the excitement of pro-opiomelanocortin (POMC) neurons and orexigenic circuits (Valassi et al., 2008). In addition to a general satiety control, PYY has been shown to modulate neural activity in the ventral tegmental area and ventral striatum (Shin et al., 2009). These modulations could affect the differences between ‘wanting’ and ‘liking’ different foods (Shin et al., 2009). PYY also may be important for decreasing food intake after RYGB (Shin et al., 2009).

Oxyntomodulin is a product of the glucagon precursor, proglucagon, released from L-cells of the intestine (Holst et al., 2018). Release is stimulated by the introduction of luminal nutrients in the intestine including carbohydrates, lipids, and proteins. Other regulators of L-cell secretion, like that of acetylcholine upon muscarinic receptors of L cells, will also modulate oxyntomodulin and GLP-1 release (Hansen et al., 2004; Holst et al., 2018). The production of pro-glucagon by L cells results in the formation of glicentin and oxyntomodulin, but rarely glucagon, as glucagon concentrations are the result of less than 1% of the total post-modulatory results of proglucagon release. Pro-glucagon can produce additional products including GLP-1 (Holst, 2007; Holst et al., 2018). These relative amounts may change after gastrointestinal surgery, notably RYGB and pancreatectomy (Holst et al., 2018).

There are no known specific receptors for oxyntomodulin, however, it is known to interact with glucagon receptor and GLP-1R but with a lower affinity than their namesake ligands (Holst et al., 2018). These receptors are located within the pancreatic islets which can be activated by oxyntomodulin potentially stimulating insulin secretion. Oxyntomodulin also demonstrated increases in glucagon secretion in vitro and in vivo human studies which are counteractive to its potential effects upon the pancreas (Holst et al., 2018). The actions of oxyntomodulin were observed to influence acid secretion from the oxyntic glands in the stomach, providing the signaling molecule its name (Bataille et al., 1982). Similar to both glucagon and GLP-1, oxyntomodulin also displays an effect on appetite control, inhibiting food intake (Holst et al., 2018). Subcutaneous injection of oxyntomodulin three times daily in humans caused a weight loss of 2.3kg in humans over four weeks (Wynne et al., 2005). It can also induce an increase in energy expenditure, and in pain-feeding experiments, the inhibition of food intake was more efficient than restrictions in food intake, suggesting that this molecule also increases energy expenditure (Dakin et al., 2002).

GLP-1 is an additional incretin released by L cells in the duodenum, and it is also produced through the cleavage of proglucagon (Berthoud, 2008; Chaudhri et al., 2006). Release is proportional to caloric intake throughout the gut, although proximal and distal gut release occur independently. This release is proportional to luminal nutrients these regions proximally and distally, though the majority of L-cells are located in the distal gut (Chaudhri et al., 2006; Roberge and Brubaker, 1991). Following vagotomy, the influence of fat intake upon GLP-1 release was eliminated, indicating that vagal afferent stimulus is also necessary for the release of GLP-1 (Rocca and Brubaker, 1999).

GLP-1 immunoreactive neurons can be found within the paraventricular nucleus (PVN), NTS, and the dorsomedial nucleus of the hypothalamus (Chaudhri et al., 2006; Valassi et al., 2008). In these areas it induces a satiating effect in conjunction with other released proglucagon factors. It can enhance glucose-induced stimulation of insulin synthesis and secretion. It also reduces glucagon release and delays gastric emptying (Valassi et al., 2008). Obese individuals, after a carbohydrate heavy meal, display a reduced release of GLP-1 postprandially when compared to control matched lean individuals (Ranganath et al., 1996).

It has been suggested that GLP-1 be utilized as an anti-obesity drug however its clinical practicality is limited by its short half-life, lasting only 1-3 minutes before being inactivated by dipeptidyl peptidase IV (Valassi et al., 2008). Targeted intravenous infusion of exendin-1, an agonist of GLP-1, was followed by a 21% decrease in daily food intake with reductions in fasting and post-prandial glucose levels (Bray, 2006).

Growth hormone secretagogue receptor (GHSR) preceded ghrelin's discovery. GHSR is a g-protein coupled receptor located in the anterior pituitary and hypothalamus. It is responsible for raising intracellular calcium concentrations in neurons and stimulating the release of growth hormone(Yin et al., 2009). Additionally, the activation of GHSR has an orexigenic response and regulates energy metabolism and appetite in neurological tissues(Yin et al., 2009). Furthermore, GHSR has been shown to elicit action stimulated by ghrelin in other organ systems including the gastroenteropancreatic system, cardiovascular system, reproductive system, and immune system (Yin et al., 2009).

Of the signals produced by the alimentary canal, ghrelin is of interest because it is the only known hormone inducing an orexigenic response(Kojima et al., 1999; Muller et al., 2015; Yin et al., 2009). Ghrelin, a 28 amino acid peptide hormone, originally discovered by Kojima and colleagues in 1999, is the only known endogenous orexigenic hormone (Kojima et al., 1999). Levels rise in between meals during periods of fasting on a regular diurnal cycle (Kojima et al., 1999).

The ghrelin gene, located on chromosome 3p25-26, encodes for pre-proghrelin which is composed of 117 amino acid residues (Yin et al., 2009). This gene contains 4 introns and 5 exons however the regulation mechanism for transcription remains largely unknown though there is some linkage to the circadian rhythm (Iijima et al., 2021; Yin et al., 2009). The protein produced from this gene is pre-proghrelin, which can be post-translationally modified into ghrelin and obestatin (Yin et al., 2009). Ghrelin is produced in the des-acyl form, largely in the gastric mucosa. However, it is also found in a variety of tissues including the hypothalamus, pituitary gland, hippocampus, brain cortex, adrenal gland, intestine, pancreas, and other tissues (Yin et al., 2009). The highest concentrations of ghrelin production occur in the fundus of the stomach by P/D1 endocrine cells, also known as X/A-like cells, of the oxyntic mucosa (Date et al., 2000). Because they are closed type cells with no continuation with the lumen of the stomach, ghrelin cell production is theorized to be stimulated by physical input from the lumen and/or chemical stimulation from the basolateral site, acting with endocrine function (Date et al., 2000).

There are two major forms of ghrelin, n-octanoyl ghrelin and des-acyl ghrelin (Date et al., 2000; Kojima et al., 1999). Des-acyl ghrelin has less biological activity than the acylated form, but is the major form manufactured in the tissues of the stomach and small intestine (Date et al., 2000; Kojima et al., 1999) . Des-acyl ghrelin is post-translationally acylated into n-octanoyl ghrelin through the action of ghrelin o-acyl transferase (GOAT), mostly in the pancreas and stomach of humans (Date et al., 2000; Kojima et al., 1999) . GOAT attaches a fatty acid chain, utilizing the substrate Octanoyl-CoA, at the serine 3 position of des-acyl ghrelin forming N-octanoyl ghrelin. N-octanoyl ghrelin interacts with GHSR to increase intracellular Ca^{2+} concentrations in the pituitary and arcuate nucleus of the hypothalamus (Kojima et al., 1999). The action of Ghrelin within the hypothalamus drives an orexigenic effect within the arcuate nucleus and lateral hypothalamic area promoting food intake (Valassi et al., 2008).

Ghrelin production is influenced by a number of factors including macronutrient consumption, endocrine interactions, and autonomic nervous input (Cummings et al., 2001; Valassi et al., 2008). . The greatest influences in determining circulating levels of ghrelin are feeding behaviors. Ghrelin is well known to rise before a meal and fall after a meal (Cummings et al., 2001; Valassi et al., 2008). In addition to the consumption of food, specific types of food can also have a significant influence on the production levels of ghrelin (Baldelli et al., 2006; Kim et al., 2007; Toshinai et al., 2001). Glucose consumption markedly inhibits ghrelin secretion while insulin-induced hypoglycemia up-regulates ghrelin mRNA expression and increases serum acyl ghrelin levels in the stomach (Baldelli et al., 2006; Kim et al., 2007; Toshinai et al., 2001). Ingestion of medium chain fatty acids and medium-chain triacylglycerides increases acylation of ghrelin without effecting the total ghrelin levels (Yin et al., 2009). There are also differences in ghrelin modulation dependent upon the length of fatty chain, as seen from the infusion of "intralipid, a mixture of long-chain triglycerides," which decreases the plasma total ghrelin in humans (Gormsen et al., 2006). Ghrelin levels are also elevated in anorectic patients while remaining low in obese patients. In obese patients reductions in ghrelin release upon food intake are lacking (Vettor et al., 2002). Additionally, infusion of PYY can decrease circulating ghrelin in alignment with the reduction of caloric intake (Batterham et al., 2003).

The function of ghrelin in the hypothalamus is facilitated by the action of GHSR. GHSR is mainly located in the hypothalamus pituitary unit, specifically the NPY and growth hormone releasing hormone (GHRH) neurons (Valassi et al., 2008). Exogenous administration of ghrelin induces hunger in humans, and a short-term stimulus of food intake (Wren et al., 2001). This action appears to be through the interaction of these receptors through the NPY/agouti-related peptide (AGRP) pathways and the inhibition of POMC neurons (Valassi et al., 2008). Part of the signaling associated with this pathway is done through afferent vagal innervation of the NTS (Valassi et al., 2008). While it has been thought that the use of GHSR antagonists would promote weight loss, in rodents this led to paradoxical weight gain with an inhibition of growth hormone release (Halem et al., 2005).

The gastric hormones described previously show many common traits creating an integrated picture of appetite control. In addition to being synthesized by gastrointestinal tissue, many of these hormones are also synthesized in areas of the brain involved in overall caloric homeostasis. This includes the production of CCK, GLP-1 and PYY (Woods, 2004). The comprehensive integration of these signals both orexigenic and anorexigenic assist in controlling the sensations of hunger and fullness.

Adipose tissue is another very active endocrine organ that participates in the regulation of a body’s total energy state. These homeostatic functions are facilitated through the release of exogenous factors inducing leptin(Ahima et al., 1999; Miller et al., 2014; Trayhurn et al., 2006). Leptin is released from adipocytes with increases in release associated with obesity, overfeeding, and in response to various signaling molecules

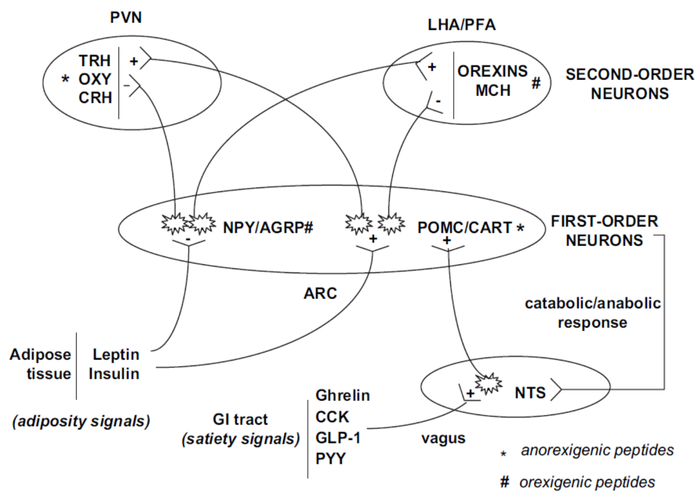
(Ahima et al., 1999). The signals increasing circulating leptin circulation include insulin, glucocorticoids, proinflammatory cytokines, and glucosamine (Ahima et al., 1999). Circulating leptin levels are proportional to an individual's amount of adipose tissue (Park and Ahima, 2015; Valassi et al., 2008). Acting through the hypothalamic-pituitary axis, leptin can regulate short-term energy intake, modulating meal size, via appetite controls. To function, leptin activates anabolic pathways while inhibiting catabolic circuits (Valassi et al., 2008). In disease states where leptin is absent, or it's receptor is ineffective, severe obesity and hyperphagia tend to occur (Ahima et al., 1999; Park and Ahima, 2015).

Signals are also produced from organ systems outside the GI tract which influence appetite and energy intake in healthy individuals (Ahima et al., 1999; Valassi et al., 2008). Adiposity signals, like leptin provide an indication of the content of adipose tissue and stored lipid within the body(Ahima et al., 1999). Leptin and insulin can send signals to the arcuate nucleus, thus simulating the release of anorexigenic peptides, and activating catabolic processes (Ahima et al., 1999; Valassi et al., 2008). Conversely, the act of the anabolic circuit releases orexigenic peptides and occurs when adiposity signals are reduced. This signaling is indicative of diminished energy stores, and drives consumption towards homeostasis (Valassi et al., 2008).

The integration of these signals is key to the collaborative effect of these controls on hunger and satiety. This comprehensive integration is accomplished through neuroendocrine signaling within different regions of the hypothalamic pituitary axis (Valassi et al., 2008). As indicated in Figure 3, appetite control is regulated by two major pathways within the hypothalamus. The arcuate nucleus is a major control center for food intake in the hypothalamus and contains two interconnected groups of first-order neurons. One group of neurons releases neuropeptide Y and agouti related peptide inducing an orexigenic effect, while the other group releases POMC and cocaine- and amphetamine-regulated transcript (CART) inducing an anorexigenic effect (Valassi et al., 2008). The satiety signaling groups of first-order neurons project to second order neurons in the paraventricular nucleus inducing their anorexigenic effects while second order neurons in the lateral hypothalamic and perifornical areas induce an orexigenic effect (Valassi et al., 2008). These pathways are outlined in Figure 3.

The anorexigenic effect is promoted through the stimulation of the paraventricular nucleus and the release of thyrotropin-releasing hormone, oxytocin, and corticotropin-releasing hormone (Valassi et al., 2008). The orexigenic pathways stimulate the lateral hypothalamic area and the peripherical area where orexins and melanin-concentrating hormone are released (Valassi et al., 2008). These central signaling molecules interact with higher brain structures to communicate general satiation and hunger signals driving the overall direction of energy balance through food intake (Valassi et al., 2008).

Figure 3. A schematic representation of the chief brain pathways involved in the regulation of eating behavior.



ARC, arcuate nucleus; NTS, solitary tract nucleus; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY. PVN, paraventricular nucleus; LHA, lateral hypothalamic area; PFA, perifornical area; NPY, neuropeptide Y; AGRP, Agouti-related peptide; POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; TRH, thyrotropin-releasing hormone; OX, oxytocin; MCH, melanin-concentrating hormone (Valassi et al., 2008)**.**

Neuroendocrine Effects of Bariatric Surgery

Bariatric surgery involves changes to the gastrointestinal morphology to reduce food intake and promote weight loss (Wolfe et al., 2016). The majority of weight loss effects are attributed to the malabsorptive or meal restricting effects of the procedures (Lo Menzo et al., 2015; Wolfe et al., 2016) However, there are additional physiological adaptations post-surgery that can contribute to weight loss (Hanusch-Enserer and Roden, 2005). Despite the intended major anatomical adaptations of bariatric surgery, driving physiological differences to induce weight loss, these anatomical changes also modulate hormone levels and downstream neuroendocrine factors. These contribute to appetite control and energy intake (Hanusch-Enserer and Roden, 2005; Holst, 2007; Holst et al., 2018).

Incretin hormones are gut hormones secreted by gut enteroendocrine cells, which are involved in inducing pancreatic secretion (Casimiro et al., 2019). These incretins, including GLP-1, PYY, CCK, and gastric inhibitory peptide (GIP), induce a satiating effect and tend to show an early exaggerated rise following RYGB procedures (Casimiro et al., 2019). Over an extended period of time, these levels slowly decrease returning to a pre-procedure baseline (Hanusch-Enserer and Roden, 2005). GLP-1 and oxyntomodulin show a marked increase following gastric bypass procedures that contributes to reduced appetite, reduced food intake, and weight loss (Holst, 2007; Holst et al., 2018). In healthy individuals, incretins are released in response to luminal nutrients in the intestine (Casimiro et al., 2019). Increased average incretin levels correlate with sensations of fullness and the stimulation of the NTS. These signals correlate with reduce energy intake and stimulate weight loss through reduced appetite (Casimiro et al., 2019).

Plasma ghrelin concentrations are complex post-procedure, displaying different variations based on the specific procedure performed (Casimiro et al., 2019). Ghrelin concentrations are typically described as reduced following RYGB, also contributing to a reduced orexigenic effect (Cummings and Shannon, 2003). In contrast, patients undergoing LAGB showed no change in fasting ghrelin levels six months post-procedure, however there was a notable rise 8 months post-procedure (Cummings and Shannon, 2003) These differences in production levels may be due to specific anatomical changes dependent upon the bariatric procedure (Casimiro et al., 2019). Because ghrelin is largely produced in the fundus of the stomach it may be possible to modulate production based on the of the adaptation of a reduced gastric pouch. This would be more in line with Date and colleagues' (2000) results that suggest that ghrelin production is stimulated by physical input to the lumen of the stomach and/or chemical stimulation. Also notable with bariatric surgery are reductions in blood glucose that occur before weight loss (Nannipieri et al., 2013). The reductions seen in metabolic disease post-procedure but before weight loss can in part be attributed to the change in the aforementioned hormonal factors, incretins, ghrelin, and others (Dimitriadis et al., 2017; Holst, 2007; Nannipieri et al., 2013).

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In alignment with the goal of obesity management, bariatric surgical procedures have evolved over time establishing different mechanisms of action and providing improved weight loss outcomes (Lo Menzo et al., 2015; Wolfe et al., 2016). Procedures have shown focus towards different aspects associated with weight loss, establishing a greater focus more recently upon metabolic intervention (Lo Menzo et al., 2015). Because of the shift in focus towards metabolic changes following bariatric intervention, it is important to recognize the progression of endocrine changes following common procedures (Lo Menzo et al., 2015). Though there are numerous procedures and associated variations, this review will focus on two specific proceedures, RYGB and sleeve gastrectomy, because they are the most common today (Dimitriadis et al., 2017).

LAGB is also a relatively common procedure, though it has been declining in occurrence over the last 10 years because of post-surgical complications and lack of effect upon metabolic activity post-procedure (Lo Menzo et al., 2015). Because of this, LAGB will be excluded from this detailed review.

Differences between RYGB and sleeve gastrectomy are most obvious at the anatomical level (as seen in figures 2 and 3) (Akkary, 2012). Most notably, sleeve gastrectomy does not involve changes to the GI tract distal to the stomach, while RYGB involves the creation of a bypassed portion of stomach and small intestine. Because of this, it is important to recognize where endocrine signals are produced and their involvement in downstream hypothalamic control as described in Table 2. (Akkary, 2012).

Table 3. Gut Hormone's Effect via the hypothalamus

Source	Hormone(s)	Effect
Distal GI (L cells)	Peptide YY GLP-1 Oxyntomodulin	Increased satiety
Pancreas (F cells)	Pancreatic polypeptide Amylin	Increased satiety
Gastric fundus	Ghrelin	Increased hunger
Proximal small intestine (I cells)	Cholecystokinin	Increased satiety

(Akkary, 2012)

Between sleeve gastrectomy and RYGB there are limited differences in hormonal production which could provide influence to weight loss (Casimiro et al., 2019). Even with these differences there are significant similarities between both procedures. At 7-year intervals post-procedure, RYGB produces a greater percentage of excess weight loss when compared to sleeve gastrectomy, however this difference is not clinically relevant based upon pre-specified equivalence margins in that study (Gronroos et al., 2021). Endocrine changes are also comparable showing similar plasma levels for GIP, CCK, insulin, leptin (Casimiro et al., 2019). A comparison of both procedures' metabolic endocrine factors is necessary to outline specific differences as these are disputed (Casimiro et al., 2019; Dimitriadis et al., 2017; Nannipieri et al., 2013).

Both sleeve gastrectomy and RYGB induce accelerated gastric emptying, and some restriction on food intake (Wolfe et al., 2016) Because of the acceleration of gastric emptying, the nutritional contents of the GI tract reach distal portions of the small intestine more quickly compared to pre-procedure. The presence of food in the lumen of the distal GI tract increases the secretion of PYY and GLP-1, incretins associated with gastric emptying and feelings of satiety, at a greater concentration than pre-procedure (Casimiro et al., 2019). This provides an endocrine explanation for weight loss and reductions in metabolic disease following both RYGB and sleeve gastrectomy, deemed the hindgut or distal gut hypothesis (Casimiro et al., 2019; Lo Menzo et al., 2015). This effect is greater in RYGB, showing an increased display of incretin production from the distal gut than that which is seen following sleeve gastrectomy (Casimiro et al., 2019). Because of the construction of the Roux limb through this procedure, contents of the intestinal tract reach the distal small intestine relatively faster than following sleeve gastrectomy and induce a larger incretin, anorexigenic effect (Casimiro et al., 2019). In addition to the satiating effects of these incretins, they do assist in reducing the effects of metabolic diseases including type 2 diabetes (Casimiro et al., 2019).

Table 4. Effects of RYGB, sleeve gastrectomy (SG), and diet-induced weight loss on incretins and hormones.

	RYGB	SG	Diet-Induced Weight Loss
Ghrelin	↓	↔ ↓	↑
PYY	↑	↑	↓
GLP-1	↑	↑	↔
GIP	↑ ↔	↑ ↔	↑ ↔
CCK	↑	↑	↓
Insulin	↑	↑	↓
Leptin	↓	↓	↓
Adiponectin	↑	↑	↑
Estrogen	↓	↓	–

Levels of GLP-1 and PYY rise after both RYGB and SG and not in diet-induced weight loss. Ghrelin levels decrease markedly after SG and increase after diet-induced weight loss. There are conflicting data regarding the change of GIP after surgical and diet-induced weight loss and ghrelin levels after RYGB. While estrogen reduction is associated with surgical weight loss and exercise-induced weight loss it does not significantly change in diet-induced weight loss.

↓ Decreased, ↑ Increased, ↔ Conflicting data, – No change.

(Casimiro et al., 2019)

The difference in circulating plasma ghrelin post-procedure is the most disputed change between both procedures. The observed differences in ghrelin are clouded as ghrelin levels do increase in between meals and decrease when food interacts with the ghrelin-producing cells of the gastric fundus (Dimitriadis et al., 2017). Because of the nature of these procedures, ghrelin releasing cells may have variable contact with ingested nutrients providing an influence upon release of ghrelin to the plasma (Dimitriadis et al., 2017).

Following RYGB some studies noted that 6 months after surgery, patients with RYGB showed a significant decrease compared to LAGB or lifestyle modifications (Fruhbeck, Diez-Caballero, et al., 2004; Fruhbeck, Rotellar, et al., 2004) Further studies show that gastric bypass was associated with reductions in 24-hour ghrelin area under the curve when compared to obese matched healthy individuals and individuals of normal weight (Cummings et al., 2002) Yet other studies also found that greater weight loss outcomes following bariatric surgery correlated with a higher degree of ghrelin suppression (Dirksen et al., 2013).

Conversely there are studies that show ghrelin increases following RYGB including Yang and colleagues (2014) who noted both acylated and des-acyl ghrelin were elevated 1 year post-procedure in humans. Zhou and colleagues (2014) also found elevated ghrelin levels in rats 12 weeks following both RYGB and sleeve gastrectomy (Dimitriadis et al., 2017).

Studies surrounding sleeve gastrectomy center on the principle of the removal of the gastric fundus (Yousseif et al., 2014). Following sleeve gastrectomy, fasting total-ghrelin decreased 40-50% which was sustained up to 5 years post-surgery (Yousseif et al., 2014). This same study also noted reductions in post-meal circulating ghrelin levels, and area under the curve circulating ghrelin following sleeve gastrectomy (Yousseif et al., 2014).

Other studies following ghrelin levels utilize obestatin as a marker of serum ghrelin following bariatric surgery (Dimitriadis et al., 2017). These studies have found that mice treated with sleeve gastrectomy produced decreased obestatin, correlating with decreased ghrelin (Zhou et al., 2014). Additionally in human studies, Siejka and colleagues (2013) were unable to demonstrate significant changes in obestatin, correlating with no significant ghrelin changes in human. This conflicting information regarding changes of ghrelin following sleeve gastrectomy procedures indicates that the directionality of ghrelin production is disputed (Dimitriadis et al., 2017; Siejka et al., 2013).

DISCUSSION

As obesity continues to be an issue in the western developed world including the United States interventions focused on management of this disease will continue to be necessary. Bariatric surgery including RYGB and sleeve gastrectomy have shown to be proven interventions successful at managing morbid obesity(Wolfe et al., 2016). The transition from more traditional restrictive bariatric procedures including LAGB to RYGB and sleeve gastrectomy reflects an understanding these procedures as endocrine interventions rather than a purely physiological processes (Lo Menzo et al., 2015). Because of this recognition of bariatric procedures as endocrine controls of appetite and eating behaviors, it becomes more important to understand the entire endocrinological picture of obese individuals.

If the downstream effects of endocrine changes following bariatric surgery are recognized as key physiological drivers of sustained weight loss, emphasis upon the endocrine changes should drive the adaptation of future procedures. This becomes challenged by the conflicting results of clinical trials associated with endocrine release following bariatric surgery (Casimiro et al., 2019; Dimitriadis et al., 2017; Nannipieri et al., 2013). Until these changes following procedures become more consistent it is difficult to ascertain true directionality and magnitude of adaptations post-procedure.

Many of the studies associated with endocrine changes following bariatric procedures have limited sample size, commonly around 10-20 participants in total (Dirksen et al., 2013; Yang et al., 2014; Yousseif et al., 2014). Expansion of sample size should result in more clinically significant results, and clarify the impact of both sleeve gastrectomy and RYGB upon ghrelin changes.

Furthermore, there is variability within the operational definitions of different procedures (Wolfe et al., 2016). Standardizing some measurements associated with bariatric procedures, like the length of the Roux limb in RYGB or capacity of the gastric pouch in sleeve gastrectomy, may help increase consistency of these outcomes while clarifying clinical interventions upon endocrine appetite controls (Wittgrove et al., 1994). This is especially pertinent in the case of ghrelin and its production from the gastric fundus, which is resected to a variable degree in these procedures (Nannipieri et al., 2013).

Despite the recognition of bariatric surgery imparting effect through neuroendocrine factors, very few studies focus upon the endocrine changes of bariatric surgery as a primary outcome. Because of this, additional research with greater specific focus comparing pre- and post-procedure conditions could be impactful. Additionally, most studies are not directly comparative between procedures. Comparing the difference in pre- and post-procedure conditions between studies would also be essential to better understanding the imparted mechanism of action.

The monitoring and measurement of endocrine changes following procedures continues to be difficult because adipose tissue is itself an active endocrine organ. The internal homeostatic mechanisms of weight management become a factor in sustained weight loss post-procedure (Berthoud et al., 2017).

Despite these challenges, both RYGB and sleeve gastrectomy induce relative increases in plasma GLP-1 and PYY post-procedure (Casimiro et al., 2019). As both these incretins display an anorexigenic effect, it is likely they play a role in the reduction of food intake following bariatric procedures attributing to sustained weight loss.

Further areas for study could include the decrease in incretin levels towards a pre-procedure baseline or the cause of those changes over time. The interaction between GLP-1R and glucagon receptor to their ligands could be another potential area of interest as potential targets for inducing weight loss.

While the post-procedural change of plasma ghrelin is not as clear, there are some studies that show stark reductions immediately following procedure in both RYGB and sleeve gastrectomy (Cummings et al., 2002; Dirksen et al., 2013; Fruhbeck, Diez-Caballero, et al., 2004; Fruhbeck, Rotellar, et al., 2004; Yousseif et al., 2014). If this were the case, this would also attribute to weight loss as ghrelin displays an orexigenic effect. Because of the variability in other findings associated with ghrelin post-procedure, it is not clear what role ghrelin plays in the reduction of weight following RYGB and sleeve gastrectomy. Establishing the correlative effect between these procedures and ghrelin could be more helpful in further understanding the mechanism of action.

CONCLUSIONS

The reduction of obesity and changes in energy maintenance following bariatric surgery is a largely endocrine process attributed to adapted release of hormones post-procedure. While some hormones show consistent changes post-procedure, attributing to weight loss and reductions of metabolic disease, there continues to be a lack of understanding when it comes the comprehensive mechanism of action. Further research is needed to continue to explain the endocrine changes following bariatric surgery as there are a variety of different controls of hunger and appetite that follow these procedures. While bariatric surgery has historically been effective to manage obesity, it is essential to further develop an understanding of the mechanism of action to promote progress among these surgical techniques.

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