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The Effect of Bariatric Surgery on Appetite Hormones and Neuronal Associations

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A literature review in the Program in Basic Medical Sciences
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The Effect of Bariatric Surgery on Appetite Hormones and Neuronal Associations

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List of Abbreviations

ARC	Arcuate Nucleus
BAI	Body Adiposity index
Band	Laparoscopic Gastric Band
BMI	Body Mass Index
BOLD	Blood Oxygenation Level Dependent contrast imaging
CART	Cocaine and Amphetamine Regulated Transcript
CNS	Central Nervous System
GABA	Gamma-Aminobutyric Acid
NPY	Neuropeptide Y
PBN	Parabrachial Nucleus
PP	Pancreatic Polypeptide
PYY	Peptide Tyrosine Tyrosine
POMC	Pro-opiomelanocortin
RYGB	Roux-En-Y Bypass
Sleeve	Sleeve Gastrectomy

Abstract

Body weight originates from a complex interplay between energy intake and expenditure. Regulation of body weight involves multiple internal systems, as well as external influences and environmental cues. Obesity is a worldwide pandemic affecting millions of individuals from a very young age. Bariatric surgery has proven to be a very effective way of losing morbidly excess body weight and maintaining healthier BMI ranges in the long term.

Bariatric surgery implements considerable hormonal changes before any difference in BMI is detected (Rubino *et al.*, 2004), suggesting that endocrine effects are a principal mechanistic action of RYGB and sleeve surgery. Gastric band surgery has been largely discontinued, as fundal surface area manipulation alone has not proven to be very effective at long-term control of energy intake and expenditure.

Functional imaging offers a unique opportunity to understand appetite and satiety changes in real time, and postprandially. Hormones concentrations may be measured and compared with adiposity, behavior, neural circuitry, and surgical intervention.

Bariatric surgery is a new field of study, beseeching more research and invoking great interest in the clinical fields of cardiovascular disease, diabetes mellitus, and osteoarthritis. The effects of obesity on political impression, career outcomes, socioeconomics, and lifestyle have been implicated in the most recent national elections and are of great importance in the quest to fully understand the impact of obesity on our lives.

Introduction

At least 400 million adults are obese globally. Obesity rates have more than doubled in the last two decades in countries such as the United States, Australia, and England (WHO, 2015).

Adiposopathy is the idea of "sick fat", an excess of adipose tissue in the body that may be a prelude for preventable diseases or further illness. The most prevalent consequences of obesity include diabetes mellitus, cardiovascular diseases, and some cancers. There is also a negative impact on quality of life that must be taken into consideration.

Surgical management of weight loss is an emerging field with much room for improvement. The number of articles about bariatric surgery available on PubMed has doubled in the last 5 years – illustrating the urgency to understand the mechanistic differences among the surgical options for treatment of obesity. Within the last few years, traditional bariatric surgery involving a gastric band has been replaced by newer techniques in many major hospital systems (Aarts *et al.*, 2014). Reduction of energy intake as a result of surgical intervention is currently the driving force behind improvement of glycemic control (Munzberg *et al.*, 2015).

Current theories spanning the relationships between hormones and obesity are overwhelming, and measured only by body fluid samples and metrics. Hormone secretions vary greatly throughout the gastrointestinal tract and blood samples are not always reliable and accurate. Furthermore, creating experimental loss of function models is not possible in humans, limiting understanding of regional hormonal effects.

To better elucidate the role of hormones in obesity, functional imaging is a new tool in body weight research. The concept of the body set point has greatly benefited from neuroimaging tools, which can offer real-time interpretations in a non-invasive manner. Functional magnetic resonance imaging (fMRI) in particular measures immediate blood flow alterations to detect activated brain areas. These blood signals can be correlated with activation in the gastrointestinal tract for a thorough understanding of the body's multifaceted responses to hunger and satiety. Correlating neural responses with biological parameters can help elucidate many of the mysteries surrounding overeating and weight management. The increased prevalence for conducting bariatric surgery has dictated the need to understand its widespread impacts on the psychological comorbidities that exist in obese patients, the physiology of energy balance, and the putative mechanisms of change in weight set point following bariatric procedures. fMRI can currently be used as a research tool, with potential to develop into a diagnostic or even therapeutic device.

Obesity Demographics

Obesity is derived from the Latin word *obesitas*, meaning "stout, fat, or plump." Obesity can be defined using the Body Mass Index (BMI), a parameter developed by Adolphe Quetelet in the 1800s in an attempt to standardize the dynamic between mass and height (Eknoyan, 2008; Locke *et al.*, 2015). The illustration below defines the body mass index using kg-meters and pound-inches classification, for a historical 'normal' group (World Health Organization, 2015).

BMI	Classification
< 18	underweight
18-25	normal weight
25-30	overweight
30-35	obese
35-40	severely obese
> 40	very severely obese

Table 1. BMI Classification

United States BMI classifications were modified in 1998, shifting the normal/overweight distinction from BMI 27.8 to BMI 25 for men, and from BMI 27.3 to BMI 25 for women (Table 1). This resulted in the reclassification of 29 million Americans from healthy to overweight (Kuczmarski and Flegal, 2000). This represents 11% of the national population, not entirely accounting for the increase in obesity during this time period (1994 US census = 263 million). National obesity rates increased from 14.5% to 30.9% from 1971 to 2000 (Flegal *et al.*, 2002). The year 2000 marked the first time in human history when the overweight portion of the population outnumbered the underweight portion (Caballero, 2007).

$$BMI = \frac{mass_{kg}}{height_{m}^2} = \frac{mass_{lb}}{height_{in}^2} \times 703$$

The World Health Organization (WHO, 2015) formally recognized obesity as a global epidemic in 1997. According to the WHO, at least 500 million adults (greater than 10% worldwide) are obese, defined by a BMI greater than 30. In 2013, 42 million children worldwide under the age of 5 were overweight or obese (from 32 million in 1990), with a projected increase to 70 million by 2025. A greater proportion of the world's population lives in countries where overweight and obesity classifications are more fatal than underweight classification. Obesity is more common among women, in urban settings, and in higher income countries. Obesity is rapidly increasing prevalence in low- and middle- income countries. Overweight and obese BMI classifications represent major risk factors for a number of chronic diseases, either caused by increased fat mass (osteoarthritis and other musculoskeletal disorders, obstructive sleep apnea, career and social discrimination) or caused by an increased number of fat cells (Pool, 2001), such as diabetes mellitus type 2, certain types of cancer (endometrial, breast and colon), cardiovascular diseases, and non-alcoholic fatty liver disease (WHO, 2015). As shown in Figure 1, the magnitude of risk can vary greatly with genetic differences (Caballero, 2007). Excess body adiposity can further alter gene expression of crucial process such as inflammation and cell cycle division (Merhi *et al.*, 2015). Overweight and obesity are linked to more deaths worldwide than underweight (WHO, 2015).

These adiposopathies, or pathologies due to increased adiposity, greatly diminish quality of life and life expectancy, in addition to negatively impacting society as a whole.

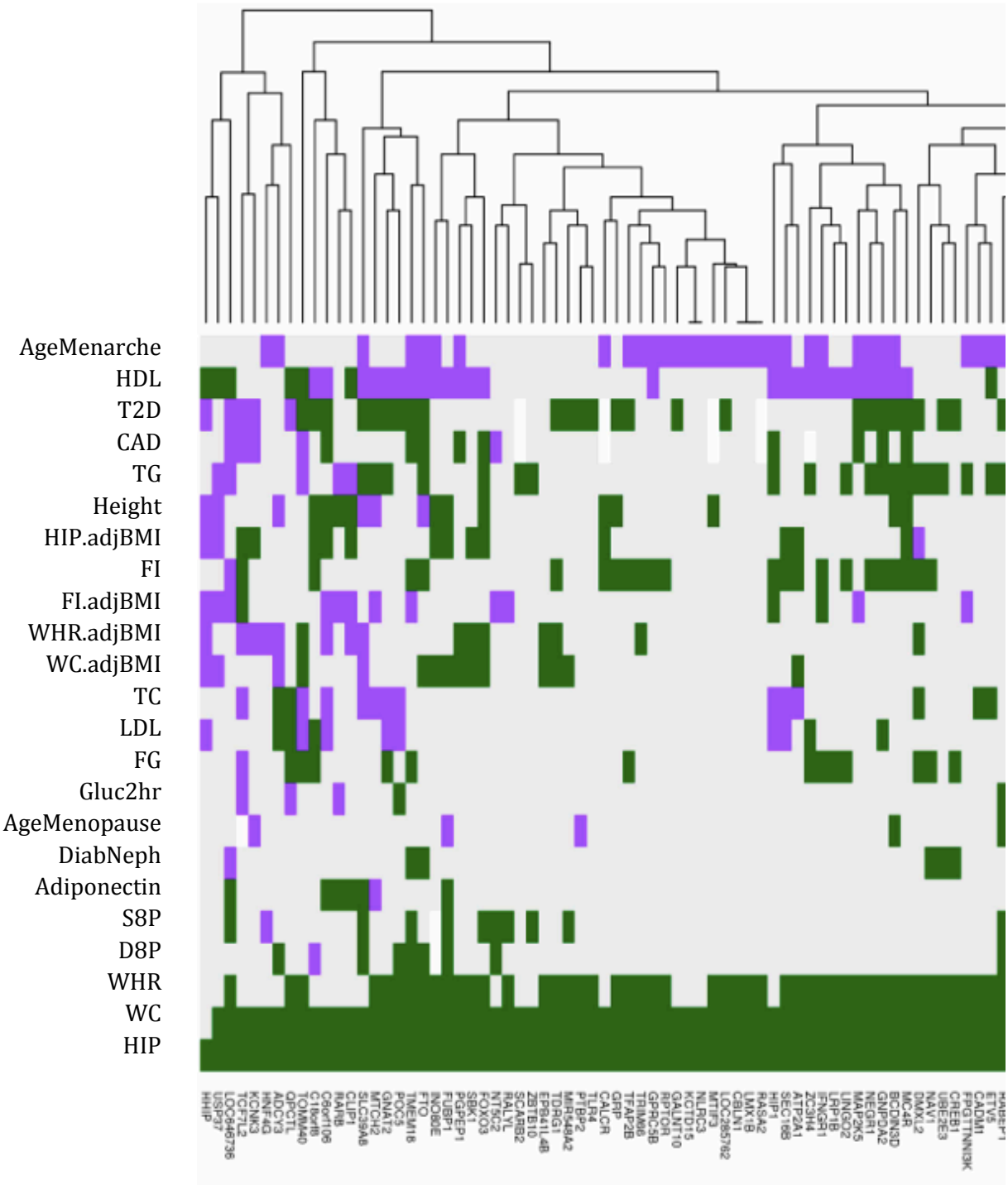

Figure 1. A meta-analysis of BMI associations with single base pair mutation loci, demonstrating the wide range of genetic effects associated with high BMI (Locke *et al.*, 2015).

Obesity: Economic Impact, Relevance

The American Medical Association classified obesity as a chronic disease in 2013 (Yanovski and Yanovski, 2014). Yet as early as the 1930s, life insurance companies were using body weight data to determine premiums, as the association between excess weight and premature death was already apparent. A direct link was proposed between obesity and cardiovascular disease in the 1950s. By the year 2000, 65% of the country's adult population had a BMI above 25, and 30% had a BMI greater than 30 (Caballero, 2007). Beyond central adiposity (BMI), liver fat and visceral fat are directly associated with metabolic syndrome, characterized by increased blood pressure, high blood sugar level, increased risk of heart disease, stroke and diabetes (Du *et al.*, 2015; Faria *et al.*, 2015).

Today, obesity is associated with 112,000 deaths per year in the United States. Over two-thirds of the adult population is overweight or obese (Chang *et al.*, 2014). A two-stage Markov cohort state transition model estimates that childhood overweight or obesity in Germany costs an additional $20,446 excess in lifetime (Sonntag *et al.*, 2015). In Michigan, the diurnal saliva samples from 269 children (mean age 50.8 months, SD 6.3) revealed blunted stress responses and increased levels of alpha amylase associated with increased BMI (Miller *et al.*, 2015).

Limitations of BMI Categorization

More recently, Body Adiposity Index (BAI) has been proposed to more accurately reflect an individual's state of excess adiposity (Bergman *et al.*, 2011; Dias *et al.*, 2013). While BMI is a ratio taking mass and height into account, it does not select for age, gender, muscle mass, bone density, type of fat tissue, or percent trunk fat. BMI is particularly inaccurate given athletic buildup of lean body mass (Bergman *et al.*, 2011; Freedman *et al.*, 2012). BAI proportionality was developed from associations of hip circumference and height with body fat percentage as measured by dual energy x-ray absorptiometry (DEXA) scans (Bergman *et al.*, 2011; Freedman *et al.*, 2012).

$$\text{Body Adiposity Index (BAI)} = \frac{\text{Hip circumference (cm)}}{\text{Height (m)}^{1.5}} - 18$$

$$\% \text{ Adiposity} = 0.93 \times \text{BAI} - 14.89$$

Since BAI as an exponent is actually a variable, it can be adjusted to reflect the nonlinear relationship between weight and height first postulated by Quetelet (Eknoyan, 2008). The relationship between BAI and adiposity percent does not appear to differ between genders (Bergman *et al.*, 2011). Still, other studies report that BMI in conjunction with waist circumference is a better indicator of body adiposity than is BAI alone (Freedman *et al.*, 2012; Geliebter *et al.*, 2013; Yu *et al.*, 2015).

As obesity is a major contributor to many diseases, treating obesity potentially improves heath in many other domains. Long-term research has shown that obesity requires persistent treatment and aggressive lifestyle changes. The US Preventive

Services Task Force recommends that physicians offer high-intensity, multicomponent behavioral interventions (Yanovski and Yanovski, 2014). In conjunction with obesity medical intervention, this is the most effective non-invasive method for clinically significant weight loss.

Treatments

(a) Lifestyle *(b) Medication (c) Surgery*

Medical consensus today suggests that obesity is largely preventable. Increased physical activity alone can significantly decrease excess body weight, as well as greatly decrease the incidence of weight-related diseases. A transition from sedentary to active energy expenditure is highly recommended, and largely resolves problems of childhood obesity, such as multiple fractures, breathing difficulties, hypertension, insulin resistance and various adult onset physical disabilities (WHO, 2015). Regular physical activity (60 minutes/day for children and 150 minutes/week for adults) is strongly encouraged. Recent evidence also suggests that food intake in obese individuals decreases after physical exercise compared to that in lean subjects (Thivel *et al.*, 2014).

A healthy lifestyle also consists of increased consumption of fruits, vegetables, legumes, whole grains and nuts, coupled with limited energy intake from fats and sugars. Currently, excess energy intake in the United States is primarily composed of carbohydrates. Sugar-sweetened beverages represent nearly 25% of daily food energy intake for young adults (Caballero, 2007). Although increased sugar consumption was introduced in the early 1900s as a means to combat malnutrition and poverty, today it causes very harmful effects such as increased BMI and malnourishment. Global food production is expected to reach 3,000 kcal per capita by the year 2030, greatly more than consumption levels (Caballero, 2007). This readily available dietary energy results in health imbalances and extreme disparities such as malnourishment and obesity in the same household (WHO, 2015). Mindful eating is necessary in order to decrease

excess carbohydrate consumption in lieu of more nutritious options. Obese individuals consistently underestimate their food consumption, as measured by calorimetry and by direct observation (Abbot *et al.*, 2008). Reducing consumption of processed foods, which often contain high quantities of sugar, fat and salt, is shown to greatly reduce excess body weight in adults (Canfi *et al.*, 2011) and children (Looney and Raynor, 2012).

Treatments

(a) Lifestyle ***(b) Medication*** *(c) Surgery*

In the United States, there are three medications currently approved for treatment of obesity. Orlistat (tetrahydrolipstatin, Xenical, Alli) is the saturated derivative of lipstatin, and was the first over the counter anti-obesity drug to be recommended by the US government (Saul, 2007). It inhibits pancreatic lipases, preventing assimilation of ingested fat. Examination of 10,000 obese individuals prescribed Orlistat for the duration of at least a year revealed an average weight loss of 2.9 kg, along with reduction in blood pressure (2 mmHg) and total cholesterol. However, HDL levels were slightly lowered and gastrointestinal side effects were prominent, including steatorrhea, fecal incontinence and urgent bowel movements. Orlistat reduced diabetes mellitus incidence from 9% to 6.2% (Padwal *et al.*, 2004). Absorption of fat soluble vitamins and nutrients is greatly reduced during use, as fat soluble vitamins are mostly esterified with a free fatty acid, therefore requiring hydrolysis by cholesterol ester hydrolase.

Lorcaserin (Belviq, Lorqess, APD-356) is an anorexigenic drug, which has serotonergic properties. It is a selective 5-HT_{2C} receptor agonist (Leonhart, 2013), hence targeting the brain's choroid plexus, hippocampus, cerebellum, amygdala, and hypothalamus. Activated 5-HT_{2C} receptors in turn activate pro-opiomelanocortin (POMC) production, which prompts satiety. In general, serotonin receptors regulate mood and endocrine secretion (Millan, 2005). Due to hallucinogenic properties at high doses, Lorcaserin is classified as a Schedule IV drug (Leonhart, 2013). A 12-week,

randomized, double-blind study of 469 subjects without diabetes mellitus showed that lorcaserin caused an average weight loss of 3.6 kg over one year. Fasting insulin and fasting glucose levels were greatly reduced, as was blood pressure and total cholesterol (Bays, 2011). Adverse side effects of Lorcaserin include headaches, upper respiratory tract infections, dizziness, and nausea. Early clinical trials found causality between medication duration and heart valve problems, but a year long Phase III clinical trial found no significant increase in heart valve problems due to daily intake of Lorcaserin (Bays, 2011). Earlier drugs, such as fenfluramine/phentermine, presented higher activation of the heart's 5-HT_{2B} receptors, and led to heart valve damage (Yanovski and Yanovski, 2014).

The third medication available in the United States, Qsymia®, is a combination of phentermine and topiramate (Yanovski and Yanovski, 2014). Phentermine is a noradrenergic sympathetic amine, and works best in short-term treatment of obesity. Topiramate is a sulfamate-substituted monosaccharide currently FDA approved for treatment of seizure disorders and prevention of migraine headaches. Data from clinical trials suggest a promotion of weight loss as well as improvement of adiposopathic consequences, which lead to metabolic diseases. According to the clinical trials data, combined administration of the two in appropriate doses presented no contraindications (Bays and Gadde, 2011). Studies indicated up to 9kg lost in weight per year with continuous use (Yanovski and Yanovski, 2014). Adverse effects include insomnia, irritability, and anxiety, expected central nervous system stimulatory symptoms, and did not differ between short-term and long-term therapy. Long-term use of Qsymia® is often prescribed off-label, and has been associated with heart

problems (Yanovski and Yanovski, 2014). Paradoxically, no weight loss medications have demonstrated a favorable effect on cardiovascular morbidity and mortality rates (Yanovski and Yanovski, 2014).

The effects of these medications on long-term obesity-related illnesses are not fully investigated. In 2011, less than 3 million people used obesity drugs in the US, a small fraction of the obese subset in the country (Yanovski and Yanovski, 2014). The research on obesity-related medications is limited, as clinical drug trials were not always previously recorded, and tend to have short durations of study period with high attrition rates. Sometimes, adverse effects are not apparent in the durations granted to pre-approval trials, or in small populations. Furthermore, most users of prescription weight loss medications are women of child bearing age, thus further research is greatly needed. Topiramate, for instance, increases risk of oral clefts in offspring according to one study (Yanovski and Yanovski, 2014). Given these limitations of curative therapies, the most effective treatment for obesity is a low-risk preventive or inhibitive measure, preventing obesity from the onset.

Treatments

(a) Lifestyle (b) Medication ***(c) Surgery***

Today, the most effective treatment for obesity is bariatric surgery. Over 200,000 operations are performed each year in the United States (Chang *et al.*, 2014). Results are very promising, with significant long-term weight loss, improvement in obesity-related medical conditions, and decreased mortality rates. Insurance

companies tend to approve coverage of bariatric surgery in cases where BMI ≥ 40, or BMI > 35 along with presence of co-morbidities, such as diabetes, respiratory illness, hypertension, cardiovascular disease, stroke, sleep apnea, and osteoarthritis (Herder *et al.*, 2014; Khaodhiar *et al.*, 1999).

The goal of therapeutic interventions, whether medical or surgical, is to improve patient health and quality of life. In addition to BMI, many factors must be taken into account to ensure an accurate benefit vs risk analysis of surgical options. Non-weight loss medications may be contributing to the high BMI of a patient, such as selective serotonin reuptake inhibitors for smoking cessation and depression. This type of antidepressant tends to increase appetite while decreasing metabolic rate (Cockerill *et al.*, 2014).

Bariatric surgery is associated with long-term weight loss, drastic improvement in obesity-related conditions, and decreased mortality rates (Chang *et al.*, 2014; Herder *et al.*, 2014). Bariatric surgery is the most effective intervention available for diabetes mellitus, resolving approximately 83% of cases (Spector and Shikora, 2010).

Surgery Types

Obesity is accompanied by chronic inflammation, prompting comorbidities such as insulin resistance, diabetes mellitus, and cardiovascular diseases. Numerous invasive interventions have been developed and therapeutically implemented. Bariatric surgeries allow restoration of hepatic and peripheral insulin sensitivity and often alleviate diabetes mellitus symptoms very soon after surgery (Lindegaard *et al.*, 2015). The bariatric surgery types discussed here are the laparoscopic adjustable gastric band (band), the Roux-en-Y gastric bypass (RYGB), and the sleeve gastrectomy (sleeve) surgeries. Although a 29% reduction in BMI has been observed 9 months after jejunoileal bypass surgery (Naslund, Gryback *et al.*, 1997), recent studies have indicated that jejunoileal bypass is not an appropriate operation for morbidly obese patients due to malnourishment and will not be integrated into the discussion.

The gastric band bariatric surgery is a simple procedure involving an elastic band fitted across the opening of the stomach, creating a 15 mL pouch (Spector and Shikora, 2010). It is a reversible procedure. The band is a useful short-term tool, but is associated with complications such as migration, erosion, prolapse, and slippage in the longer term (Domienik-Karlowicz *et al.*, 2015; Gonzalez-Heredia *et al.*, 2014; Tran *et al.*, 2013). Target weights often remain unachieved (Gonzalez-Heredia *et al.*, 2014) and revisions are required. Band procedures have given way to newer bariatric surgery types. Band removal and conversion to RYGB does not result in increased morbidity. However, the safety of band conversion to sleeve is contested, as it has been associated with major complications and mortality (Fernando Santos *et al.*, 2014) yet also deemed safe (Gonzalez-Heredia *et al.*, 2014).

RYGB surgery is the current gold standard of bariatric surgeries. A small pouch is created starting from the proximal stomach to the jejunum. This jejunostomy redirects nutrients, resulting in malabsorption (Spector and Shikora, 2010) as well as restriction (Colquitt *et al.*, 2014) as the duodenum and proximal jejunum are bypassed (Rubino *et al.*, 2004). There is a 16% internal hernia complication incidence. About 113,000 RYGB surgeries are performed each year in the United States (Livingston, 2010) including 80,000 women of childbearing age (Altieri *et al.*, 2014). By comparison, in 2001, only 33,000 RYGB surgeries were performed nationwide (Livingston, 2010). RYGB patients are at risk for malnourishment due to decreased absorptive area, decreased hydrochloric acid secretion and reduced dietary intake (Snyder-Marlow *et al.*, 2010).

Of the surgical interventions considered here, the sleeve surgery is the most extreme. 60-80% of the stomach is removed longitudinally. The remaining stomach tissue forms the shape of a sleeve, also referred to commonly as a "banana" (Figure 2). Stomach capacity is about 300 mL. The removal of the fundus serves to neurohormonally restrict food ingestion via decrease of ghrelin secretion. Sleeve surgery retains the pylorus, whereas RYGB does not preserve it. Sleeve surgery cannot be revised. There is less malabsorption after sleeve surgery as compared to that after RYGB, yet weight loss is comparable (Snyder-Marlow *et al.*, 2010). There are currently less than a decade of sleeve surgery prognoses available for consideration.

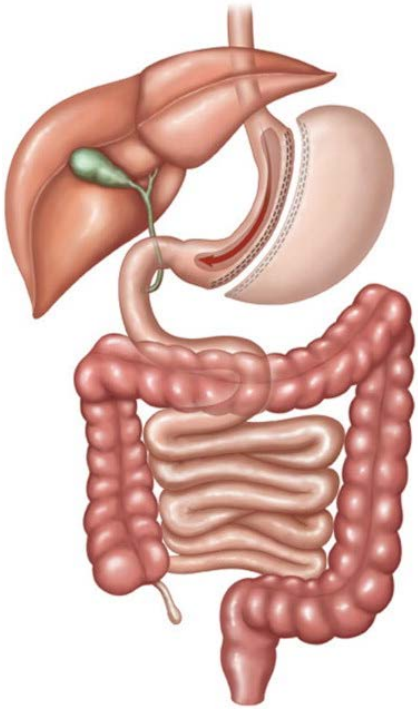

Figure 3. Sleeve gastrectomy (St. Anthony's Medical Center, 2015).

A review of 164 studies summarized bypass and sleeve weight loss 5 years postsurgery as 12 to 17 BMI units for a mean age of 44.5 years (Chang *et al.*, 2014). Noted co-morbidities included diabetes mellitus (26% of co-morbidities), hypertension (47%), dyslipidemia (28%), cardiovascular diseases (7%), and sleep apnea (25%; (Chang *et al.*, 2014). About 17% of cases experienced complications, and about 7% of these cases required reoperation. Gastric bypass surgery is linked to more weight loss and greater occurrence of complications. Sleeve gastrectomy data suggest weight loss of similar efficiency. Gastric banding has decreased mortality rates and complication rates, but less weight loss and higher incidence of reoperation (Chang *et al.*, 2014; Domienik-Karlowicz *et al.*, 2015).

Intestinal Hypertrophy

Intestinal hypertrophy post-RYGB surgery stimulates increased glucose metabolism, increasing energy expenditure and accounting for most of the resolution of diabetes 2 in this patient population (Korner *et al.*, 2009; le Roux *et al.*, 2010; Munzberg *et al.*, 2015; Saeidi *et al.*, 2013). There is strong evidence of glucose transporter-1 upregulation, as well as increases in basolateral glucose uptake and aerobic glycolysis. Glucose is redirected toward tissue growth pathways following exposure of the Roux limb to undigested nutrients. In rats, Glucagon-like peptide-2 (GLP-2) levels demonstrate a 91% increase after RYGB surgery, and crypt cell proliferation is significant. GLP-2, a proteolytic cleavage of pro-glucagon that resembles GLP-1, is transported to the brain where it binds to the Neuropeptide Y/Agouti-related peptide or POMC receptors in the hypothalamus to elicit satiety. Human GLP-2 levels 6 months after RYGB surgery peaked at 168% of pre-operative levels, strongly suggesting restoration of absorptive surface area (le Roux *et al.*, 2010). Current research, although limited, indicates no correlation between intestinal hypertrophy and sleeve gastrectomy surgery (Mumphrey *et al.*, 2015). Sleeve gastrectomy and RYGB both show increased levels of fibroblast growth factors 19 and 21 after surgery (Cummings *et al.*, 2012; Jansen *et al.*, 2011). In mice, these growth factors stimulate increased energy expenditure via thermogenesis in brown adipose tissue (Watanabe *et al.*, 2006). Energy intake relative to output is the main determinant for weight gain or loss, even after bariatric surgery (Ortega *et al.*, 2012). While it is difficult to distinguish biological need from behavioral modification in humans, animal models are useful for the study of energy intake and output after bariatric surgery.

Energy Intake and Expenditure

Human studies report that energy intake (i.e., ingestion) is reduced to half of pre-operative levels within 6 months of RYGB surgery, and stabilizes at about 40% (of initial) after a few years. Metabolizable energy (i.e., net absorption) after surgery is further reduced with a decrease in the efficiency of fat absorption. Human studies indicate a substantial decrease in fat absorption efficiency after RYGB, averaging a 22% decrease in noted studies (Odstrcil *et al.*, 2010). In consideration of total metabolizable energy (total intake less the amount malabsorbed), the contribution of malabsorption to total energy levels after surgery is relatively small (Odstrcil *et al.*, 2010).

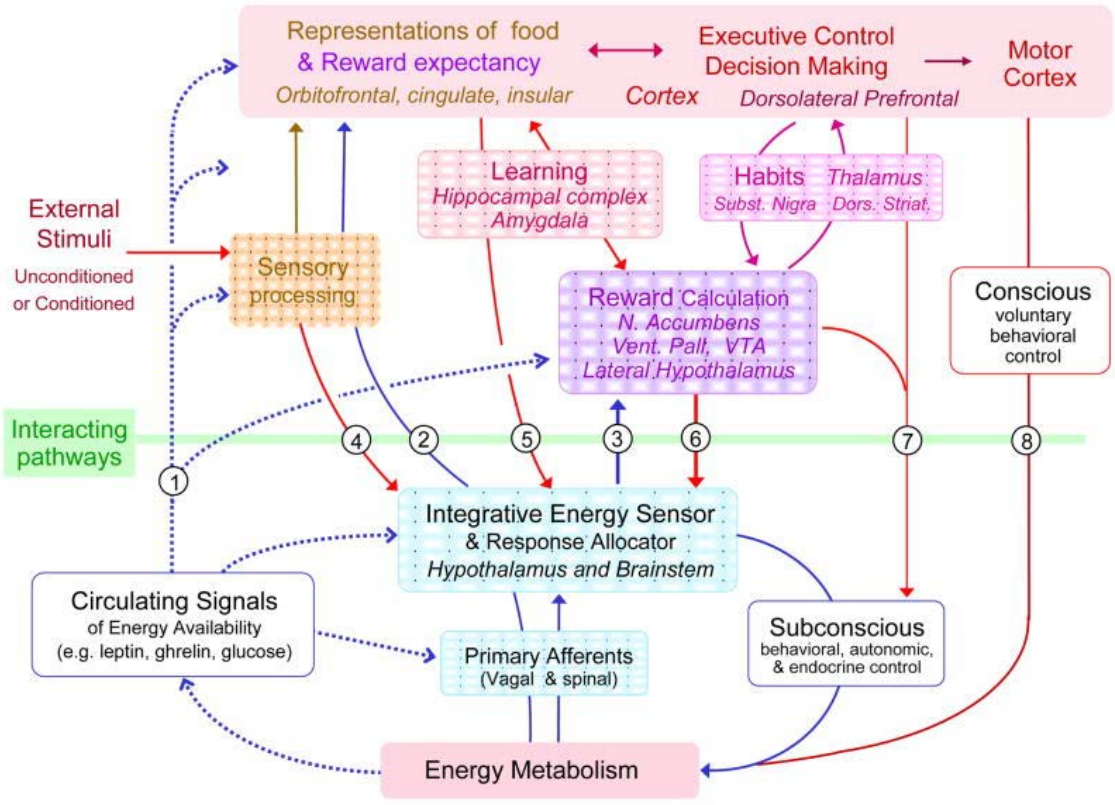

Figure 3. Reward calculations incorporate many different signals. (Berthoud, 2011)

The biomechanisms of food intake include internal and external cues that provoke a decision of whether to eat or stop eating (Figures 3 and 4). There are signal processing components that individuals are aware of, as well as inside processes. Previous reward food cues, for example, can intensify hunger and initiate ingestion (Figure 4). The homeostatic regulators of energy balance in the hypothalamus-brain stem axis also emphasize a certain level of adiposity and body weight for the individual. These are governed by genetic and environmental cues that influence hormonal and neural feedback mechanisms. Berthoud demonstrates the complexity of varying signals from the external and internal milieu. As shown in Figure 3, this investigation takes into account changes in food intake, autonomic and endocrine responses, nutrient partitioning, energy expenditure, and hormonal and neural mechanisms that contribute to adaptive energy expenditure:

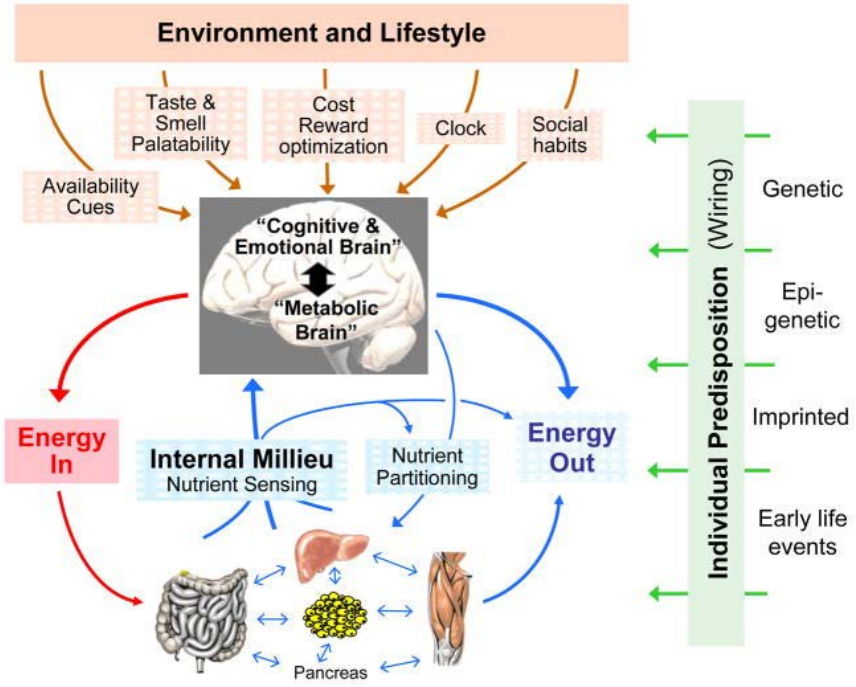

Figure 4. Energy expenditure relies on multiple factors that span the genetic and environmental milieu. (Berthoud, 2011)

Since energy expenditure is so closely associated with body weight and food intake, the next logical step is to examine changes to energy expenditure as a result of bariatric surgery. Of great interest is the body's internal, non-caloric reaction to the significant weight change, and any adherence to a weight set-point after surgery.

In rat studies, animals undergoing sleeve gastrectomy demonstrated an adherence to pre-surgery body weight when permitted access to unlimited food (Stefater *et al.*, 2011). However, in pregnant rats that received sleeve gastrectomy, the animals gained weight after surgery but returned to pre-pregnancy weight after delivery (Grayson *et al.*, 2013). In RYGB rats, food intake was artificially increased via central melanocortin-3/4 receptor signaling blockade, which resulted in increased body weight. When the blockade was removed, the rats returned to their lower body weight (Munzberg *et al.*, 2015). This indicates that rats are able to increase food intake physically, but respond to cues that enable them to adhere to a pre-surgery set point.

Neuroimaging

Set point regulation is not completely understood. The therapeutic potential of bariatric surgery hinges upon a greater understanding of how the body adheres to a pre-surgery set point. Neuroimaging offers a unique opportunity through which neural responses to food and food stimuli can be monitored. It is a non-invasive, low-risk tool that can nonetheless measure sensitive real time changes in the body and brain. Neuroimaging can be used to detect changes in real time, and can be paired with visual, auditory, olfactory, and tactile stimuli in order to simulate realistic outcomes. Data can be normalized within and between subject populations, and selected regions of interest (ROI) can average signal activation across populations for a greater confidence interval and lower deviation across results. Relevant results include activations in areas such as premotor planning, visual and gustatory sensory input, and reward pathway.

Functional MRI scanning can detect regional changes in blood oxygenation levels as determined by blood oxygen level dependent contrast imaging (BOLD signals). Increased perfusion of oxygenated blood denotes increased neuronal activity for given brain regions. These BOLD signals are easily quantified using software that distinguishes these findings from coincidences using voxel limits, a type of pixel that quantifies the magnitude of BOLD signaling in very small slices of the brain (Carnell *et al.*, 2012; Carnell *et al.*, 2014).

A recent study using neuroimaging suggests a set point commonality amongst RYGB patients after surgery. Female RYGB patients were compared with obese women who did not undergo bariatric surgery. Stimuli included food and non-food visual cues.

Hunger and satiety were rated using a visual analog scale at regular intervals. As compared to the RYGB group, the obese group demonstrated stronger functional connectivity in the frontal region and higher hypothalamic activation during presentation of food cues. Furthermore, RYGB patients had lower scores of hunger and higher scores of satiety on the visual analog rating as compared to the non-surgery obese group. These findings strongly suggest that surgery can alter the pre-surgery set point (Frank *et al.*, 2014).

Further Investigation of Brain Peptides

Select basomedial hypothalamic peptides can reliably indicate hunger states because of their strong impact on homeostatic regulation. Agouti-related peptide (AgRP) is a paracrine signaling molecule similar to Agouti signaling peptide (25% amino acid homology). It is synthesized in the neurons of Neuropeptide Y (NPY)-containing cell bodies of the arcuate nucleus in the hypothalamus. AgRP is usually co-expressed with NPY (Loh *et al.*, 2015). It functions to decrease energy expenditure (metabolism) and increase appetite by inhibiting sensations of satiety (Flier, 2004). The appetite-stimulating effect is inhibited by leptin and enhanced by ghrelin. When leptin is secreted by adipocytes in response to food intake, AgRP prevents release of orexigenic peptides. NPY/AgRP neurons express ghrelin receptors that can stimulate NPY and AgRP co-secretion. AgRP stimulates the hypothalamic-pituitary-adrenocortical axis to release ACTH, cortisol and prolactin (Bugarith *et al.*, 2005). Further investigation of the relationship among AgRP secretion, satiety, and hunger may help elucidate set point changes that occur after surgery.

The arcuate nucleus contains two distinct groups of neurons. A second basomedial hypothalamic peptide closely linked with homeostatic regulation, and consequently set point, originates from the pro-opiomelanocortin (POMC) and the cocaine and amphetamine regulated transcript (CART) expressing neurons. These neurons have stimulatory inputs to the ventromedial nucleus (feeling of fullness), and inhibitory inputs to the lateral hypothalamus (food motivation, attraction to eating behavior). In the dual center hypothesis of eating, a combination of these two centers

contributes to overall healthy levels of eating. Studies demonstrate hyperphagia in rats following lateral hypothalamus lesions, while lesions of the ventromedial nucleus result in increased plasma insulin levels and overproduction of leptin, leading to leptin desensitization and overeating (Flier, 2004). The POMC/CART neurons oppose the effects of NPY/AgRP neurons. In addition to feeding and regulation of energy expenditure, the peripheral component of the NPY system, namely, white adipose tissue and osteoblasts in the periphery, has been identified as a contributor to whole body energy homeostasis (Loh *et al.*, 2015).

Hormones

A complex interplay of neurotransmitters, hormones, secretory factors and genes can contribute to greater energy intake than expenditure. An imbalance between energy intake and expenditure leads to overweight and obesity. While some of these systems have been meticulously explored, many questions still remain. Weight loss therapies focusing on calorie restriction are largely ineffective. An overview of recent research regarding central (CNS) and peripheral (body) factors is implicated in obesity.

Bariatric surgery has been extremely effective in treating diabetes mellitus, and is currently being considered as a preventive process as well (Herder *et al.*, 2014; Munzberg *et al.*, 2015). It is important to understand the role that appetite hormones play in micro niches of the stomach and intestines. Hormones are released during, prior to, in lack of, and after ingestion of nutrients. Bariatric surgery may offer decreased gastrointestinal lumen surface area (sleeve, RYGB), leading to malabsorption. Removal of the fundus in particular leads to a significant decrease in ghrelin secretion, and subsequently, appetite.

Gastrointestinal hormone changes are divided into three categories: obtunded responses (ghrelin/leptin), normal release (motilin, adiponectin), and increased secretion (PYY). Gastrointestinal hormones are numerous and complex; here, each category of hormone is examined in connection to bariatric surgery effects.

Hormones: NPY

As mentioned previously, the neuropeptide Y system promotes feeding (appetite) and reduces energy expenditure. Other family members, peptide YY (PYY) and pancreatic polypeptide (PP), mediate satiety levels in an extensive network of homeostatic regulation.

As the hypothalamus is the center of appetite control and energy balance, nuclei crosstalk is often complex and seemingly contradictory, appearing at times to promote opposite physiological effects. Feeding stimuli from NPY neurons and orexigenic stimuli from AgRP neurons activate downstream pathways via distinct receptors (a potential regulating mechanism in itself) and communication with the paraventricular nucleus, ventromedial nucleus, dorsomedial hypothalamus, and lateral hypothalamic area (Loh *et al.*, 2015). NPY neurons also co-express the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA).

NPY is a 36 amino acid peptide abundantly found in the central and peripheral nervous system. It is expressed in the hypothalamus, cerebral cortex, brainstem, adrenal glands, white adipose tissue, and osteoblasts (Loh *et al.*, 2015). PYY and PP are produced in the intestinal L cells and pancreatic PP cells, respectively. Although largely co-expressed, all three are ligands for separate G-protein coupled receptors, inhibiting secondary messenger system cAMP production in target cells, which include the liver, skeletal muscle, immune cells, and pancreas (Loh *et al.*, 2015).

The blood-brain barrier is semi-permeable and arcuate nucleus (ARC) neurons are able to respond rapidly to hormonal signals from the periphery, such as leptin, insulin, ghrelin, and satiety factors PYY and PP by relaying signals to previously

mentioned brain areas. Leptin from adipose tissue and insulin from pancreatic beta cells circulate in proportion to whole body adiposity and inhibit NPY/AgRP neuronal activity. They also stimulate POMC/CART neuronal activity in order to inhibit food intake. By contrast, ghrelin from the stomach and duodenum activate the NPY/AgRP neurons to promote food intake.

A distinct neural projection has been identified from ARC NPY/AgRP neurons to oxytocin neurons in the PBN (Loh *et al.*, 2015). Genetic deletion of NPY, AgRP, or both has not resulted in feeding inhibition, suggesting compensatory mechanisms exist that regulate and maintain energy expenditure and homeostasis (Figure 5). This mechanism potentially involves NPY/AgRP GABA signaling as rat studies have shown a tendency toward anorexia when GABA co-expression is lost. This may be due to a nausea signal activated by the parabrachial nucleus (PBN). ARC NPY signaling has also been shown to decrease brown adipose tissue thermogenesis by direct downregulation of uncoupling protein-1. Targeting of uncoupling protein-1 has been suggested as a treatment option for adult obesity. A role for NPY in energy homeostasis has been less well understood (Loh *et al.*, 2015).

The effects of bariatric surgery on the NPY system have been studied in animal models. 6 weeks after surgery, sleeve populations demonstrate lower PYY, increased hypothalamic NPY, and higher POMC levels than band populations (Kawasaki *et al.*, 2015). This supports the understanding that NPY promotes appetite and PYY regulates satiety, as the lumen in sleeve surgery is much smaller than that of the band post-op stomach. Both groups however show marked improvement over sham-operated controls. There is ample evidence indicating that in addition to stomach alteration,

sleeve surgery also modifies the neuronal circuitry involved in eating behavior, leading to improved outcomes than in band surgery.

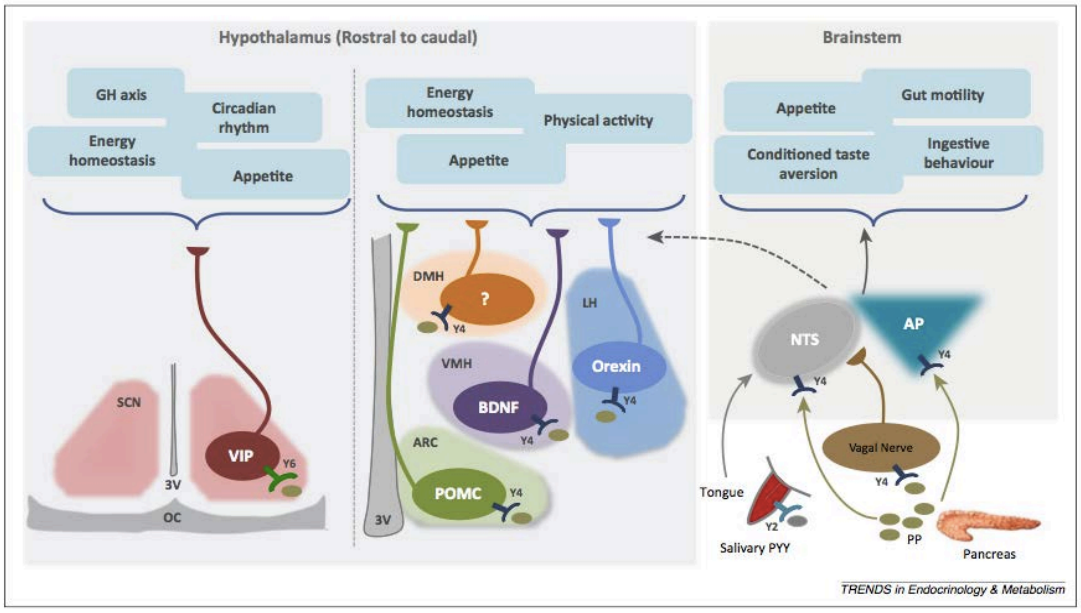

Figure 5. The NPY signaling system involves multiple pathways implicated in feeding. Among others, orexin directly interacts with NPY and POMC in a manner reciprocal to leptin. (Loh *et al.*, 2015)

Hormones: Adiponectin

Adiponectin is the most abundant gastrointestinal hormone within plasma, representing 0.01% of serum protein concentration. Adiponectin improves glycemic control by regulating glucose uptake, decreasing gluconeogenesis and influencing fatty acid oxidation. Adiponectin levels increase following weight loss (Coppola *et al.*, 2009) or bariatric surgery (Herder *et al.*, 2014; Lindegaard *et al.*, 2015; Malin *et al.*, 2014 (Herder *et al.*, 2014), most notably with RYGB and sleeve (Buzga *et al.*, 2014), suggesting possible pathways involved in diabetes mellitus control. The hormone is

reduced in instances of diabetes and increased in females relative to that in males (Lim *et al.*, 2014).

Adiponectin is abundantly produced by adipocytes during caloric restriction and thus correlates inversely with body fat percentage (Ukkola and Santaniemi, 2002) and with BMI (Lindegaard *et al.*, 2015). The mechanism(s) causing downregulation of adiponectin in obese subjects is (are) not known. However, post translational pathways have been suspected. Adiponectin is capable of forming low molecular weight (LMW) trimers, middle molecular weight (MMW) hexamers and high molecular weight (HMW) 12-18-mers. Multimer formation is an important mechanism that regulates the biological activity of adiponectin in that different target tissues respond to these distinct oligomers. For example, of the three multimers, the HMW isoform is more metabolically active and closely associated with peripheral insulin sensitivity. Hence, depending on the metabolic status or disease condition the proportions of the oligomers can change. In type-2 diabetics, HMW adiponectin selectively decreases. Resveratrol, a polyphenolic stilbenoid derivative found in certain foods, e.g., grapes, exhibits anti-diabetic properties and appears to protect against obesity-related downregulation of adiponectin. Thiazolidinediones and resveratrol promote multimerization via upregulation of disulfide bond (Liu and Liu, 2012). Reduction of the high molecular weight form of adiponectin is associated with various metabolic diseases states (Domienik-Karlowicz *et al.*, 2015), suggesting that enhancement of adiponectin multimerization helps treat insulin resistance. After bariatric surgery, patients show marked improvements in diabetes mellitus status, as measured by various metabolic determinants. Rises in adiponectin levels are observed, mediating

both insulin action as well as adipose mass, for up to two years after surgery (Malin *et al.*, 2014), particularly in the case of sleeve surgery (Buzga *et al.*, 2014).

Hormones: The 'Gut Clock'

As our understanding of the enteric nervous system grows, implications for the body's circadian rhythm must also be considered. Daily food intake is greatly influenced by biological rhythms (Konturek *et al.*, 2011). The suprachiasmatic nucleus serves as the central pacemaker and communicates bidirectionally with tissues.

Transcriptional and translational feedback loops govern periodic activity of gut segments via interstitial cells. Neuroendocrine cells of the gut mucosa produce melatonin, affecting food intake and myoelectric rhythm. In addition to the regulatory effects of melatonin on gastric motility, a recent study suggests that melatonin is beneficial in alleviating abdominal pain and distention.

Disruption of circadian rhythm in the gut has been shown to result in gastrointestinal pathology such as irritable bowel syndrome, gastroesophageal reflux disease, peptic ulcers, as well as acceleration of aging and tumorigenesis of the liver and gastrointestinal tract. Disruption of gastric rhythms can result in overeating and subsequent excess weight gain (Konturek *et al.*, 2011). Most notably, shifting of food intake schedules strongly correlates with weight gain (Konturek *et al.*, 2011).

Disruptions to the 'gut clock' have been shown to improve markedly following weight loss or bariatric surgery, reestablishing eating patterns and behaviors and gastric motility.

Hormones: Ghrelin and Leptin

Ghrelin and leptin are complementary hormones influencing appetite. Ghrelin is produced in the stomach for short-term control and is sensitive to stomach distention (Wierup *et al.*, 2007). Secreted mostly in the oxyntic region (Wierup *et al.*, 2007), ghrelin increases gastric emptying and stimulates appetite. Adipose cells for mediation of long-term appetite control produce leptin. Leptin is greatly increased in obese individuals, who are thought to be resistant to the hormone. Administration of leptin in these individuals does not suppress appetite (Flier, 2004).

Leptin and ghrelin are produced peripherally and exhibit feeding and satiety effects on the hypothalamus; namely, the arcuate nucleus to the lateral and ventromedial hypothalamus (Boulpaep, 2003). As mentioned previously, the NPY/AgRP neurons stimulate feeding and inhibit satiety, while the POMC/CART neurons exert the opposite effects. Leptin inhibits the former two hormones and stimulates the latter two (Flier, 2004). Thus, decreasing desire to eat. Higher plasma leptin levels are generally correlated with prevention of cognitive decline, but severely obese individuals tend to develop leptin resistance, leading to a decrease of leptin control on feeding behavior (Alosco *et al.*, 2015).

Following bariatric surgery, reduced inflammation and better glycemic control are noted (Alosco *et al.*, 2015; Arismendi *et al.*, 2014; Domienik-Karlowicz *et al.*, 2015). The improved ghrelin and leptin levels 12 months after surgery have been shown to influence cognitive improvements as well (Alosco *et al.*, 2015). Prior to surgery, increased leptin levels have correlated with worse attention and executive function performance (inhibition, emotional eating, and snacking control); this is rectified after

bariatric surgery in the same patient population. Increased ghrelin is also associated with better attention and executive function (Alosco *et al.*, 2015). Mechanisms may include reduced inflammation and improved glycemic control (Alosco *et al.*, 2015; Arismendi *et al.*, 2014). Bariatric surgery can potentially increase the brain's sensitivity to leptin by decreasing leptin resistance, leading to reduced risk of cognitive decline and dementia (Alosco *et al.*, 2015). Fasting plasma leptin levels decrease markedly following bariatric surgery, sometimes within a week (Lindegaard *et al.*, 2015). Sleeve studies specifically manifest decrease of ghrelin and leptin levels one year after surgery, with no significant difference in appetite (Buzga *et al.*, 2014).

The ghrelin/leptin imbalance in obesity is greatly improved by bariatric surgery. Leptin resistance is also decreased, with overall better brain health outcomes with regards to inhibition and emotional eating, cognitive benefits and snacking control.

Hormones: Motilin

Motilin exhibits structural homology to ghrelin, an appetite stimulatory peptide produced in the stomach (Asakawa *et al.*, 2001). Motilin is located throughout the gut, and increases gastric emptying and small bowel motility. Like ghrelin, it demonstrates pro-kinetic properties, and is not secreted postprandially. Because motilin is not secreted postprandially, it does not seem to affect loss of gastric function due to surgery (Yamashita *et al.*, 1997). Motilin and ghrelin are stored in the same secretory granules (93%) of the duodenal and jejunal mucosa. Co-secretion is further supported by evidence of parallel increases of ghrelin and motilin in plasma profiles (Wierup *et al.*, 2007).

Motilin is increased in obese individuals following jejunoileal bypass (Naslund, Melin *et al.*, 1997) and other gastrectomies (Ohira, 1988). The rate of gastric emptying is not significantly different (Naslund *et al.*, 1997), lending credibility to the suggestion that ghrelin may function independently of motilin (Wierup *et al.*, 2007).

Gastric resection surgeries tend to be accompanied by loss of gastric motor function. Gastric resection promotes reflux esophagitis, malabsorption, and dumping syndrome, an unpleasant, unsettled feeling that can result in flatulence, heartburn, emesis, abdominal cramps, nausea, and diarrhea. As one patient described dumping syndrome, "a heart attack with food poisoning" (personal communication, 2014).

Hormones: GLP-1

Glucagon-like peptide-1 (GLP-1) is released from ileal L cells within minutes of food ingestion. Its half-life is less than two minutes until degradation. GLP-1 is an anti-hyperglycemic hormone, stimulating insulin secretion and suppressing glucagon secretion, while increasing satiety signaling in the brain. Long-term GLP-1 receptor activation is linked to weight loss (Baggio and Drucker, 2007).

GLP-1 can be induced in laboratory animals by inflammatory stimuli such as treatments with endotoxin, interleukins 1 and 6, and circulating GLP-1 itself (Lindegaard *et al.*, 2015). Postprandial GLP-1 secretion is increased immediately after RYGB surgery (Ohira, 1988), but does not sustain long term (Lindegaard *et al.*, 2015). By contrast, GLP-1 is increased one year after sleeve surgery (Kawasaki *et al.*, 2015). While interleukin 6 decreases after surgery (Figure 6), it is higher in diabetic patients after surgery, suggesting a role in glycemic control. Most notably, interleukin 8 changes

correlate positively with GLP-1 concentration (Lindegaard *et al.*, 2015). Interleukin 8 is closely associated with peripheral inflammation. It is especially relevant to the pathogenesis of atherosclerosis and cardiovascular diseases. Pro-inflammatory molecules such as interleukins 6 and 8 are secreted at high levels by adipose tissue (Domienik-Karlowicz *et al.*, 2015). RYGB surgery decreases fasting plasma concentrations of pro-inflammatory cytokine interleukin 6 within a year after surgery, or even earlier (Lindegaard *et al.*, 2015). GLP-1 changes after surgery may be the reason behind changes in taste bud reception, as GLP-1 receptors are found in mammalian taste buds. A reduction in sweet gustational sensitivity is observed in GLP-1 knockout mice, suggesting an important paracrine function of GLP-1 in bariatric surgery (Martin *et al.*, 2009).

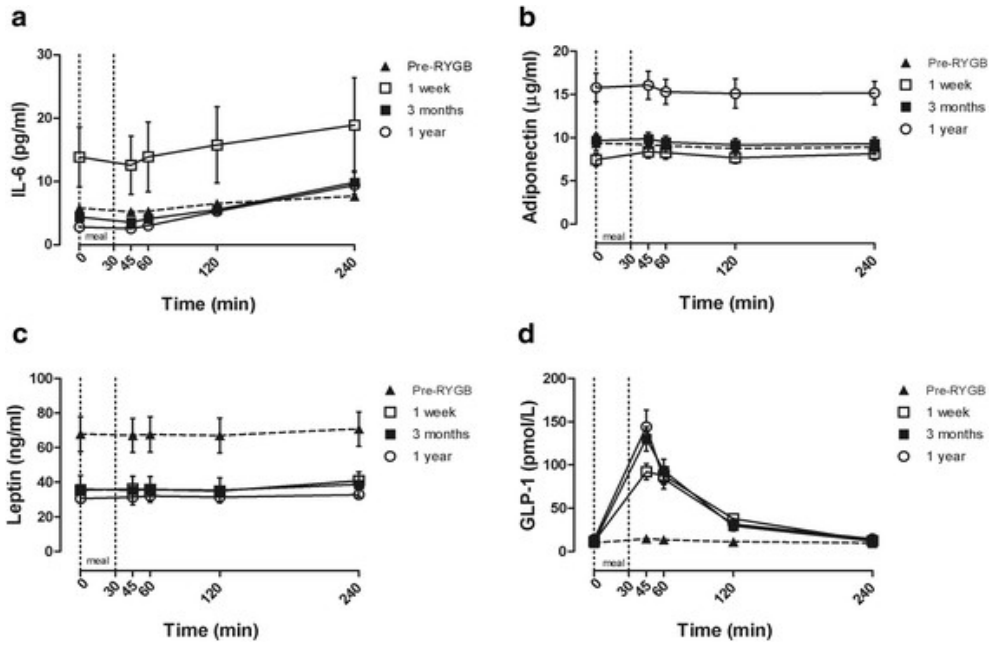

Figure 6. Postprandial cytokine and GLP-1 response before and after RYGB surgery (one week, three months, one year; adapted from Lindegaard *et al*, 2015).

Conclusion

Bariatric surgery involving resection of the gastrointestinal tract induces weight loss through slowed emptying rate, decreased stomach capacity, malabsorption of fat, and prohibited intake of calorie dense foods. This is a marked improvement upon gastric band surgery, which does not exhibit many endocrine effects in comparison. Bariatric surgery data suggest a major shift in hormonal secretions is imperative for greater weight loss success.

Bariatric surgery has demonstrated a series of effects on many gastrointestinal hormones. Noted here are the increase in NPY and decrease in PYY and PP, promoting an appetite and satiety signaling pathway less conducive to overeating. Adiponectin, an important protein found abundantly in the plasma, increases after weight loss or bariatric surgery, assisting in better glycemic control. The suprachiasmatic nucleus' regulation of eating schedules is severely disrupted in obesity, and restored within a few months of surgical intervention. Increased melatonin production also assists in the restoration of the 'gut clock' and gastric motility. Ghrelin levels are decreased following all types of bariatric surgery and leptin resistance is decreased as well which leads to l healthier hunger/satiety cycle. Motilin is increased after weight loss or bariatric surgery, assisting in various components of the gastric motility and digestion pathway. Finally, GLP-1 levels are increased, manifested by decreases in chronic inflammation by various cytokines. Inflammatory reduction is associated with marked improvements in obesity-related co-morbidities such as atherosclerosis and cardiovascular diseases.

Careful observation of biometrics immediately following bariatric surgery has shown that hormonal changes occur rapidly and much earlier than changes in BMI

values (Rubino *et al.*, 2004). This is strong evidence that supports improvements of endocrine dysregulation observed with RYGB and sleeve surgery. Gastric band surgery is much less common, as lumen surface area and intestinal pathways are not modified. Functional imaging technologies offer a rare glimpse into the gastrointestinal pathways and disruptions hallmarked by obesity. fMRI studies have successfully demonstrated correlations between neuronal secretions and appetite ratings, as well as BMI and other weight metrics. There is great potential for elucidation of body mechanisms using functional MRI and other imaging techniques.

Further research is proposed to measure hormonal changes before and after bariatric surgery using neuroimaging. To understand the specific role of surgery, time points must include immediate effects after surgery, prior to significant BMI changes, as well as long term data.

References

Aarts E, Koehestanie P, Dogan K, Berends F, Janssen I. 2014. Revisional surgery after failed gastric banding: Results of one-stage conversion to RYGB in 195 patients. *Surg Obes Relat Dis.* 10:1077-1083.

Abbot JM, Thomson CA, Ranger-Moore J, Teixeira PJ, Lohman TG, Taren DL, Cussler E, Going SB, Houtkooper LB. 2008. Psychosocial and behavioral profile and predictors of self-reported energy underreporting in obese middle-aged women. *J Am Diet Assoc.* 108:114-119.

Alosco ML, Spitznagel MB, Strain G, Devlin M, Cohen R, Crosby RD, Mitchell JE, Gunstad J. 2015. Improved serum leptin and ghrelin following bariatric surgery predict better postoperative cognitive function. *J Clin Neurol.* 11:48-56.

Altieri MS, Telem DA, Kim P, Gracia G, Pryor AD. 2014. Case review and consideration for imaging and work evaluation of the pregnant bariatric patient. *Surg Obes Relat Dis.* 14:S1550-7289.

Arismendi E, Rivas E, Agusti A, Rios J, Barreiro E, Vidal J, Rodriguez-Roisin R. 2014. The systemic inflammome of severe obesity before and after bariatric surgery. *PLoS One.* 9:e107859.

Asakawa A, Inui A, Kaga T, Yuzuriha H, Nagata T, Ueno N, Makino S, Fujimiya M, Niijima A, Fujino MA, Kasuga M. 2001. Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motilin. *Gastroenterology.* 120:337-345.

Baggio LL, Drucker DJ. 2007. Biology of incretins: GLP-1 and GIP. *Gastroenterology.* 132:2131-2157.

Bays HE. 2011. Lorcaserin: Drug profile and illustrative model of the regulatory challenges of weight-loss drug development. *Expert Rev Cardiovasc Ther.* 9:265-277.

Bays HE, Gadde KM. 2011. Phentermine/topiramate for weight reduction and treatment of adverse metabolic consequences in obesity. *Drugs Today (Barc).* 47:903-914.

Bergman RN, Stefanovski D, Buchanan TA, Sumner AE, Reynolds JC, Sebring NG, Xiang AH, Watanabe RM. 2011. A better index of body adiposity. *Obesity (Silver Spring).* 19:1083-1089.

Berthoud HR. 2011. Metabolic and hedonic drives in the neural control of appetite: Who is the boss? *Curr Opin Neurobiol.* 21:888-896.

Boulpaep E. *Medical Physiology: A Cellular and Molecular Approach.* 1st ed. Philadelphia: Saunders; 2003.

Bugarith K, Dinh TT, Li AJ, Speth RC, Ritter S. 2005. Basomedial hypothalamic injections of neuropeptide Y conjugated to saporin selectively disrupt hypothalamic controls of food intake. *Endocrinology.* 146:1179-1191.

Buzga M, Zavadilova V, Holeczy P, Svagera Z, Svorc P, Foltys A, Zonca P. 2014. Dietary intake and ghrelin and leptin changes after sleeve gastrectomy. *Wideochir Inne Tech Malo Inwazyjne.* 9:554-561.

Caballero B. 2007. The global epidemic of obesity: An overview. *Epidemiol Rev.* 29:1-5.

Canfi A, Gepner Y, Schwarzfuchs D, Golan R, Shahar DR, Fraser D, Witkow S, Greenberg I, Sarusi B, Vardi H, Friger M, Stampfer MJ, Shai I. 2011. Effect of changes in the intake of weight of specific food groups on successful body weight loss during a multi-dietary strategy intervention trial. *J Am Coll Nutr.* 30:491-501.

Carnell S, Benson L, Pantazatos SP, Hirsch J, Geliebter A. 2014. Amodal brain activation and functional connectivity in response to high-energy-density food cues in obesity. *Obesity (Silver Spring).* 22:2370-2378.

Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. 2012. Neuroimaging and obesity: Current knowledge and future directions. *Obes Rev.* 13:43-56.

Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. 2014. The effectiveness and risks of bariatric surgery: An updated systematic review and meta-analysis, 2003-2012. *JAMA Surg.* 149:275-287.

Cockerill RG, Biggs BK, Oesterle TS, Croarkin PE. Antidepressant use and body mass index change in overweight adolescents: A historical cohort study. *Innov Clin Neurosci.* 11:14-21.

Colquitt JL, Pickett K, Loveman E, Frampton GK. 2014. Surgery for weight loss in adults. *Cochrane Database Syst Rev.* 8:CD003641.

Cummings BP, Bettaieb A, Graham JL, Stanhope KL, Kowala M, Haj FG, Chouinard ML, Havel PJ. 2012. Vertical sleeve gastrectomy improves glucose and lipid metabolism and delays diabetes onset in UCD-T2DM rats. *Endocrinology.* 153:3620-3632.

Dias IB, Panazzolo DG, Marques MF, Paredes BD, Souza MG, Manhanini DP, Morandi V, Farinatti PT, Bouskela E, Kraemer-Aguiar LG. 2013. Relationships between emerging cardiovascular risk factors, z-BMI, waist circumference and body adiposity index (BAI) on adolescents. *Clin Endocrinol (Oxf).* 79:667-674.

Domienik-Karlowicz J, Rymarczyk Z, Dzikowska-Diduch O, Lisik W, Chmura A, Demkow U, Pruszczyk P. 2015. Emerging markers of atherosclerosis before and after bariatric surgery. *Obes Surg.* 25:486-493.

Du T, Yu X, Zhang J, Sun X. 2015. Lipid accumulation product and visceral adiposity index are effective markers for identifying the metabolically obese normal-weight phenotype. *Acta Diabetol.* Feb 19. [Epub ahead of print].

Eknoyan G. 2008. Adolphe quetelet (1796-1874)--the average man and indices of obesity. *Nephrol Dial Transplant.* 23:47-51.

Faria G, Goncalves A, Cunha R, Guimaraes JT, Calhau C, Preto J, Taveira-Gomes A. 2015. Beyond central adiposity: Liver fat and visceral fat area are associated with metabolic syndrome in morbidly obese patients. *Int J Surg.* 14:75-79.

Fernando Santos B, Wallaert JB, Trus TL. 2014. Band removal and conversion to sleeve or bypass: Are they equally safe? *Surg Endosc.* 28:3086-3091.

Flegal KM, Carroll MD, Ogden CL, Johnson CL. 2002. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA.* 288:1723-1727.

Flier JS. 2004. Obesity wars: Molecular progress confronts an expanding epidemic. *Cell.* 116:337-350.

Frank S, Wilms B, Veit R, Ernst B, Thurnheer M, Kullmann S, Fritsche A, Birbaumer N, Preissl H, Schultes B. 2014. Altered brain activity in severely obese women may recover after roux-en Y gastric bypass surgery. *Int J Obes (Lond).* 38:341-348.

Freedman DS, Thornton JC, Pi-Sunyer FX, Heymsfield SB, Wang J, Pierson RN,Jr, Blanck HM, Gallagher D. 2012. The body adiposity index (hip circumference / height(1.5)) is not a more accurate measure of adiposity than is BMI, waist circumference, or hip circumference. *Obesity (Silver Spring).* 20:2438-2444.

Geliebter A, Atalayer D, Flancbaum L, Gibson CD. 2013. Comparison of body adiposity index (BAI) and BMI with estimations of % body fat in clinically severe obese women. *Obesity (Silver Spring).* 21:493-498.

Gonzalez-Heredia R, Masrur M, Patton K, Bindal V, Sarvepalli S, Elli E. 2014. Revisions after failed gastric band: Sleeve gastrectomy and roux-en-Y gastric bypass. *Surg Endosc.* Nov 27. [Epub ahead of print].

Grayson BE, Schneider KM, Woods SC, Seeley RJ. 2013. Improved rodent maternal metabolism but reduced intrauterine growth after vertical sleeve gastrectomy. *Sci Transl Med.* 5(199):199ra112.

Herder C, Peltonen M, Svensson PA, Carstensen M, Jacobson P, Roden M, Sjostrom L, Carlsson L. 2014. Adiponectin and bariatric surgery: Associations with diabetes and cardiovascular disease in the swedish obese subjects study. *Diabetes Care.* 37:1401-1409.

Jansen PL, van Werven J, Aarts E, Berends F, Janssen I, Stoker J, Schaap FG. 2011. Alterations of hormonally active fibroblast growth factors after roux-en-Y gastric bypass surgery. *Dig Dis.* 29:48-51.

Kawasaki T, Ohta M, Kawano Y, Masuda T, Gotoh K, Inomata M, Kitano S. 2015. Effects of sleeve gastrectomy and gastric banding on the hypothalamic feeding center in an obese rat model. *Surg Today.* Feb 28. [Epub ahead of print].

Khaodhiar L, McCowen KC, Blackburn GL. 1999. Obesity and its comorbid conditions. *Clin Cornerstone.* 2:17-31.

Konturek PC, Brzozowski T, Konturek SJ. 2011. Gut clock: Implication of circadian rhythms in the gastrointestinal tract. *J Physiol Pharmacol.* 62:139-150.

Korner J, Inabnet W, Febres G, Conwell IM, McMahon DJ, Salas R, Taveras C, Schrope B, Bessler M. 2009. Prospective study of gut hormone and metabolic changes after adjustable gastric banding and roux-en-Y gastric bypass. *Int J Obes (Lond).* 33:786-795.

Kuczmarski RJ, Flegal KM. 2000. Criteria for definition of overweight in transition: Background and recommendations for the united states. *Am J Clin Nutr.* 72:1074-1081.

le Roux CW, Borg C, Wallis K, Vincent RP, Bueter M, Goodlad R, Ghatei MA, Patel A, Bloom SR, Aylwin SJ. 2010. Gut hypertrophy after gastric bypass is associated with increased glucagon-like peptide 2 and intestinal crypt cell proliferation. *Ann Surg.* 252:50-56.

Leonhart M. **Drug Enforcement Administration - Schedules of Controlled Substances: Placement of Lorcaserin Into Schedule IV**. Available at: https://www.federalregister.gov/articles/2013/05/08/2013-10895/schedules-of-controlled-substances-placement-of-lorcaserin-into-schedule-iv. Accessed January/27, 2015.

Lim S, Quon MJ, Koh KK. 2014. Modulation of adiponectin as a potential therapeutic strategy. *Atherosclerosis.* 233:721-728.

Lindegaard KK, Jorgensen NB, Just R, Heegaard PM, Madsbad S. 2015. Effects of roux-en-Y gastric bypass on fasting and postprandial inflammation-related parameters in obese subjects with normal glucose tolerance and in obese subjects with type 2 diabetes. *Diabetol Metab Syndr.* 7:12-015-0012-9. eCollection 2015.

Liu M, Liu F. 2012. Up- and down-regulation of adiponectin expression and multimerization: Mechanisms and therapeutic implication. *Biochimie.* 94:2126-2130.

Livingston EH. 2010. The incidence of bariatric surgery has plateaued in the U.S. *Am J Surg.* 200:378-385.

Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, Croteau-Chonka DC, Esko T, Fall T, Ferreira T, Gustafsson S, Kutalik Z, Luan J, Magi R, Randall JC, Winkler TW, Wood AR, Workalemahu T, Faul JD, Smith JA, Hua Zhao J, Zhao W, Chen J, Fehrmann R, Hedman AK, Karjalainen J, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bolton JL, Bragg-Gresham JL, Buyske S, Demirkan A, Deng G, Ehret GB, Feenstra B, Feitosa MF, Fischer K, Goel A, Gong J, Jackson AU, Kanoni S, Kleber ME, Kristiansson K, Lim U, Lotay V, Mangino M, Mateo Leach I, Medina-Gomez C, Medland SE, Nalls MA, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Shungin D, Stancakova A, Strawbridge RJ, Ju Sung Y, Tanaka T, Teumer A, Trompet S, van der Laan SW, van Setten J, Van Vliet-Ostaptchouk JV, Wang Z, Yengo L, Zhang W, Isaacs A, Albrecht E, Arnlov J, Arscott GM, Attwood AP, Bandinelli S, Barrett A, Bas IN, Bellis C, Bennett AJ, Berne C, Blagieva R, Bluher M, Bohringer S, Bonnycastle LL, Bottcher Y, Boyd HA, Bruinenberg M, Caspersen IH, Ida Chen YD, Clarke R, Daw EW, de Craen AJ, Delgado G, Dimitriou M, Doney AS, Eklund N, Estrada K, Eury E, Folkersen L, Fraser RM, Garcia ME, Geller F, Giedraitis V, Gigante B, Go AS, Golay A, Goodall AH, Gordon SD, Gorski M, Grabe HJ, Grallert H, Grammer TB, Grassler J, Gronberg H, Groves CJ, Gusto G, Haessler J, Hall P, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heard-Costa NL, Helmer Q, Hengstenberg C, Holmen O, Hottenga JJ, James AL, Jeff JM, Johansson A, Jolley J, Juliusdottir T, Kinnunen L, Koenig W, Koskenvuo M, Kratzer W, Laitinen J, Lamina C, Leander K, Lee NR, Lichtner P, Lind L, Lindstrom J, Sin Lo K,

Lobbens S, Lorbeer R, Lu Y, Mach F, Magnusson PK, Mahajan A, McArdle WL, McLachlan S, Menni C, Merger S, Mihailov E, Milani L, Moayyeri A, Monda KL, Morken MA, Mulas A, Muller G, Muller-Nurasyid M, Musk AW, Nagaraja R, Nothen MM, Nolte IM, Pilz S, Rayner NW, Renstrom F, Rettig R, Ried JS, Ripke S, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Schumacher FR, Scott WR, Seufferlein T, Shi J, Vernon Smith A, Smolonska J, Stanton AV, Steinthorsdottir V, Stirrups K, Stringham HM, Sundstrom J, Swertz MA, Swift AJ, Syvanen AC, Tan ST, Tayo BO, Thorand B, Thorleifsson G, Tyrer JP, Uh HW, Vandenput L, Verhulst FC, Vermeulen SH, Verweij N, Vonk JM, Waite LL, Warren HR, Waterworth D, Weedon MN, Wilkens LR, Willenborg C, Wilsgaard T, Wojczynski MK, Wong A, Wright AF, Zhang Q, LifeLines Cohort Study, Brennan EP, Choi M, Dastani Z, Drong AW, Eriksson P, Franco-Cereceda A, Gadin JR, Gharavi AG, Goddard ME, Handsaker RE, Huang J, Karpe F, Kathiresan S, Keildson S, Kiryluk K, Kubo M, Lee JY, Liang L, Lifton RP, Ma B, McCarroll SA, McKnight AJ, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Okada Y, Perry JR, Dorajoo R, Reinmaa E, Salem RM, Sandholm N, Scott RA, Stolk L, Takahashi A, Tanaka T, Van't Hooft FM, Vinkhuyzen AA, Westra HJ, Zheng W, Zondervan KT, ADIPOGen Consortium, AGEN-BMI Working Group, CARDIOGRAMplusC4D Consortium, CKDGen Consortium, GLGC, ICBP, MAGIC Investigators, MuTHER Consortium, MIGen Consortium, PAGE Consortium, ReproGen Consortium, GENIE Consortium, International Endogene Consortium, Heath AC, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Blangero J, Bovet P, Campbell H, Caulfield MJ, Cesana G, Chakravarti A, Chasman DI, Chines PS, Collins FS, Crawford DC, Cupples LA, Cusi D, Danesh J, de Faire U, den Ruijter HM, Dominiczak AF, Erbel R, Erdmann J, Eriksson JG, Farrall M, Felix SB, Ferrannini E, Ferrieres J, Ford I, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gejman PV, Gieger C, Gottesman O, Gudnason V, Gyllensten U, Hall AS, Harris TB, Hattersley AT, Hicks AA, Hindorff LA, Hingorani AD, Hofman A, Homuth G, Hovingh GK, Humphries SE, Hunt SC, Hypponen E, Illig T, Jacobs KB, Jarvelin MR, Jockel KH, Johansen B, Jousilahti P, Jukema JW, Jula AM, Kaprio J, Kastelein JJ, Keinanen-Kiukaanniemi SM, Kiemeney LA, Knekt P, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimaki T, Lyssenko V, Mannisto S, Marette A, Matise TC, McKenzie CA, McKnight B, Moll FL, Morris AD, Morris AP, Murray JC, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Madden PA, Pasterkamp G, Peden JF, Peters A, Postma DS, Pramstaller PP, Price JF, Qi L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Rioux JD, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schunkert H, Schwarz PE, Sever P, Shuldiner AR, Sinisalo J, Stolk RP, Strauch K, Tonjes A, Tregouet DA, Tremblay A, Tremoli E, Virtamo J, Vohl MC, Volker U, Waeber G, Willemsen G, Witteman JC, Zillikens MC, Adair LS, Amouyel P, Asselbergs FW, Assimes TL, Bochud M, Boehm BO, Boerwinkle E, Bornstein SR, Bottinger EP, Bouchard C, Cauchi S, Chambers JC, Chanock SJ, Cooper RS, de Bakker PI, Dedoussis G, Ferrucci L, Franks PW, Froguel P, Groop LC, Haiman CA, Hamsten A, Hui J, Hunter DJ, Hveem K, Kaplan RC, Kivimaki M, Kuh D, Laakso M, Liu Y, Martin NG, Marz W, Melbye M, Metspalu A, Moebus S, Munroe PB, Njolstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Perusse L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sattar N, Schadt EE, Schlessinger D, Slagboom PE, Snieder H, Spector TD, Thorsteinsdottir U, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Walker M, Wallaschofski H, Wareham NJ, Watkins H, Weir DR, Wichmann HE, Wilson JF, Zanen P, Borecki IB, Deloukas P, Fox CS, Heid IM, O'Connell JR, Strachan DP, Stefansson K, van Duijn CM, Abecasis GR, Franke L, Frayling TM, McCarthy MI, Visscher PM, Scherag A, Willer CJ, Boehnke M, Mohlke KL, Lindgren CM, Beckmann JS, Barroso I, North KE, Ingelsson E, Hirschhorn JN, Loos RJ, Speliotes EK. 2015. Genetic studies of body mass index yield new insights for obesity biology. *Nature.* 518:197-206.

Loh K, Herzog H, Shi YC. 2015. Regulation of energy homeostasis by the NPY system. *Trends Endocrinol Metab.* 26:125-135.

Looney SM, Raynor HA. 2012. Are changes in consumption of "healthy" foods related to changes in consumption of "unhealthy" foods during pediatric obesity treatment? *Int J Environ Res Public Health.* 9:1368-1378.

Malin SK, Bena J, Abood B, Pothier CE, Bhatt DL, Nissen S, Brethauer SA, Schauer PR, Kirwan JP, Kashyap SR. 2014. Attenuated improvements in adiponectin and fat loss characterize type 2 diabetes non-remission status after bariatric surgery. *Diabetes Obes Metab.* 16:1230-1238.

Martin B, Dotson CD, Shin YK, Ji S, Drucker DJ, Maudsley S, Munger SD. 2009. Modulation of taste sensitivity by GLP-1 signaling in taste buds. *Ann N Y Acad Sci.* 1170:98-101.

Merhi Z, Polotsky AJ, Bradford AP, Buyuk E, Chosich J, Phang T, Jindal S, Santoro N. 2015. Adiposity alters genes important in inflammation and cell cycle division in human cumulus granulosa cells. *Reprod Sci.* Feb 11. [Epub ahead of print].

Millan MJ. 2005. Serotonin 5-HT2C receptors as a target for the treatment of depressive and anxious states: Focus on novel therapeutic strategies. *Therapie.* 60:441-460.

Miller AL, Sturza J, Rosenblum K, Vazquez DM, Kaciroti N, Lumeng JC. 2015. Salivary alpha amylase diurnal pattern and stress response are associated with body mass index in low-income preschool-aged children. *Psychoneuroendocrinology.* 53:40-48.

Mumphrey MB, Hao Z, Townsend RL, Patterson LM, Berthoud HR. 2015. Sleeve gastrectomy does not cause hypertrophy and reprogramming of intestinal glucose metabolism in rats. *Obes Surg.* Jan 8. [Epub ahead of print].

Munzberg H, Laque A, Yu S, Rezai-Zadeh K, Berthoud HR. 2015. Appetite and body weight regulation after bariatric surgery. *Obes Rev.* 16 Suppl 1:77-90.

Naslund E, Gryback P, Hellstrom PM, Jacobsson H, Holst JJ, Theodorsson E, Backman L. 1997. Gastrointestinal hormones and gastric emptying 20 years after jejunoileal bypass for massive obesity. *Int J Obes Relat Metab Disord.* 21:387-392.

Naslund E, Melin I, Gryback P, Hagg A, Hellstrom PM, Jacobsson H, Theodorsson E, Rossner S, Backman L. 1997. Reduced food intake after jejunoileal bypass: A possible association with prolonged gastric emptying and altered gut hormone patterns. *Am J Clin Nutr.* 66:26-32.

Odstrcil EA, Martinez JG, Santa Ana CA, Xue B, Schneider RE, Steffer KJ, Porter JL, Asplin J, Kuhn JA, Fordtran JS. 2010. The contribution of malabsorption to the reduction in net energy absorption after long-limb roux-en-Y gastric bypass. *Am J Clin Nutr.* 92:704-713.

Ohira Y. 1988. An experimental study on the remnant gastric motilities and gastrointestinal hormones after various types of gastrectomies. *Nihon Heikatsukin Gakkai Zasshi.* 24:79-100.

Ortega J, Ortega-Evangelio G, Cassinello N, Sebastia V. 2012. What are obese patients able to eat after roux-en-Y gastric bypass? *Obes Facts.* 5:339-348.

Padwal R, Li SK, Lau DC. 2004. Long-term pharmacotherapy for obesity and overweight. *Cochrane Database Syst Rev.* 3:CD004094.

Pool R, ed. *Fat: Fighting the Obesity Epidemic.* Oxfordshire: Oxford University Press; 2001.

Rubino F, Gagner M, Gentileschi P, Kini S, Fukuyama S, Feng J, Diamond E. 2004. The early effect of the roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. *Ann Surg.* 240:236-242.

Saeidi N, Meoli L, Nestoridi E, Gupta NK, Kvas S, Kucharczyk J, Bonab AA, Fischman AJ, Yarmush ML, Stylopoulos N. 2013. Reprogramming of intestinal glucose metabolism and glycemic control in rats after gastric bypass. *Science.* 341:406-410.

Saul S. Weight-Loss Drug to be Sold Over the Counter. Available at: http://www.nytimes.com/2007/02/07/health/07cnd-diet.html?_r=1&. Accessed February/10, 2007.

Snyder-Marlow G, Taylor D, Lenhard MJ. 2010. Nutrition care for patients undergoing laparoscopic sleeve gastrectomy for weight loss. *J Am Diet Assoc.* 110:600-607.

Sonntag D, Ali S, Lehnert T, Konnopka A, Riedel-Heller S, Konig HH. 2015. Estimating the lifetime cost of childhood obesity in Germany: Results of a markov model. *Pediatr Obes.* Jan 22. [Epub ahead of print].

Spector D, Shikora S. 2010. Neuro-modulation and bariatric surgery for type 2 diabetes mellitus. *Int J Clin Pract Suppl.* 166:53-58.

St. Anthony's Medical Center. Bariatric Surgery. Available at: http://www.stanthonysmedcenter.com/surgery/bariatric.asp. Accessed 03/21, 2015.

Stefater MA, Sandoval DA, Chambers AP, Wilson-Perez HE, Hofmann SM, Jandacek R, Tso P, Woods SC, Seeley RJ. 2011. Sleeve gastrectomy in rats improves postprandial lipid clearance by reducing intestinal triglyceride secretion. *Gastroenterology.* 141:939-949.

Thivel D, Metz L, Julien A, Morio B, Duche P. 2014. Obese but not lean adolescents spontaneously decrease energy intake after intensive exercise. *Physiol Behav.* 123:41-46.

Tran TT, Pauli E, Lyn-Sue JR, Haluck R, Rogers AM. 2013. Revisional weight loss surgery after failed laparoscopic gastric banding: An institutional experience. *Surg Endosc.* 27:4087-4093.

Ukkola O, Santaniemi M. 2002. Adiponectin: A link between excess adiposity and associated comorbidities? *J Mol Med (Berl).* 80:696-702.

Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, Messaddeq N, Harney JW, Ezaki O, Kodama T, Schoonjans K, Bianco AC, Auwerx J. 2006. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature.* 439:484-489.

Wierup N, Bjorkqvist M, Westrom B, Pierzynowski S, Sundler F, Sjolund K. 2007. Ghrelin and motilin are cosecreted from a prominent endocrine cell population in the small intestine. *J Clin Endocrinol Metab.* 92:3573-3581.

World Health Organization. World Health Organization #311: Obesity and Overweight. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/. Accessed February/16, 2015.

Yamashita Y, Toge T, Adrian TE. 1997. Gastrointestinal hormone in dumping syndrome and reflux esophagitis after gastric surgery. *J Smooth Muscle Res.* 33:37-48.

Yanovski SZ, Yanovski JA. 2014. Long-term drug treatment for obesity: A systematic and clinical review. *JAMA.* 311:74-86.

Yu Y, Wang L, Liu H, Zhang S, Walker SO, Bartell T, Wang X. 2015. Body mass index and waist circumference rather than body adiposity index are better surrogates for body adiposity in a chinese population. *Nutr Clin Pract.* Jan 23. [Epub ahead of print].