The Homeostatic Mechanisms of Obesity
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Abstract

This paper examines the mechanisms that maintain body weight homeostasis in humans. Obesity is increasing at rapid rates in all age groups, achieving epidemic proportions. While single gene mutations cause morbid obesity and can easily be treated: however, most cases of obesity involve a genetic predisposition in which the phenotype is expressed through environmental factors. The modern environment creates a setting that promotes and perpetuates obesity and overweight.

The hypothalamus is the section of the brain that controls food regulation and weight balance. The arcuate nucleus, ventromedial hypothalamus, lateral hypothalamus, paraventricular nucleus, and the dorsomedial hypothalamus are all important parts of the hypothalamus that are involved in weight homeostasis. These centers contain receptors for neuropeptides such as leptin, neuropeptide Y, Ghrelin, α-MSH, and CCK which can either stimulate or inhibit food intake and energy expenditure, depending on their nature.

These hypothalamic regions and neuropeptides create a negative feedback loop which regulates body weight. This negative feedback loop defends body weight, regardless of whether it is obese, lean, or underweight. The body can handle small, brief perturbations in body weight, resetting the weight back to normal. However, chronic perturbations from body weight result in a seemingly irreversible state of body weight. This review examines all mechanism involved in the maintenance and defense of body weight and possible treatments and research directions.
Introduction

Obesity has become a significant problem past thirty years and now has reached epidemic portions in most industrialized countries (Dixon and O’Brien, 2002). This prevalence of obesity has earned the name of “the disease of the twenty-first century” (Friedman, 2004). Worldwide, 1.1 billion people are either overweight or obese (Dixon and O’Brien, 2002) and 8 billion people are morbidly obese (Chen et al, 2004). In the United States, 61% of adults are overweight and 27% are obese, doubling the amount of obesity cases from twenty years ago (Dixon and O’Brien, 2002). Other highly overweight countries include Russia (54%), Brazil (36%), and China (29.5%). Obesity can lead to severe medical consequences and can cause premature death if a treatment plan is not staged. Complications related to obesity cause 275,000 to 325,000 deaths in United States each year. Obesity is the second leading cause of preventable diseases, while smoking related complications is the first leading cause of preventable disease with 400,000 deaths in the United States each year. Obesity is well on its way to becoming the greatest predictor of death in the United States (Dixon and O’Brien, 2002).

This disease not only affects adults, but is increasing in all age groups and is affecting all ethnicities. Since 1980, the number of obese children has doubled and the number of obese adolescents has tripled (Montague, 2003). Prevalence of obesity and overweight is highest among minority women, with the exception of Asian American women, who have the lowest percentage affected (Montague, 2003). In the United States, 25% of women and 18% of men are obese (Bray, 1998). Low socioeconomic status (SES) is correlated with higher levels of obesity in women, but socioeconomic status is no predictor of obesity in men (Montague, 2003).
An overweight condition transitions to obesity when surpluses of fat collect and begin to adversely affect health. The Body Mass Index (BMI) is the standard used to evaluate the presence and severity of obesity (Dixon and O’Brien, 2002). To calculate one’s BMI, weight in kilograms is divided by height in meters squared (kg/m²) (National Center for Health Statistics, 1999). A BMI from 18 to 25 is considered normal body weight, a BMI of 25 to 30 is overweight, a BMI of 30 to 40 is obesity, and a BMI over 40 is extreme obesity (National Institute of Health, 1998). A BMI over 30 defines obesity according to both the World Health Organization and the National Institute of Health. By these standards, 27% of Americans are obese and an additional 34% are overweight (National Center for Health Statistics, 1999). BMI is based on the correlation between BMI and mortality; at a BMI of 30, the risk of mortality increases by 30% and at a BMI of over 40, the risk of premature death related to obesity is 100% (Manson et al, 1995).

The epidemic of obesity adversely affects social, psychological, and economical aspects, as well as health concerns. Obesity creates a loss of productivity and mobility. Billions of dollars each year are spent on diet programs, exercise equipment, and dietary products. Obesity consumes 10% of all medical expenses (Antonio et al, 2005), which results in approximately $99.2 billion per year (Montague, 2003). Many people tend to eat in response to sadness, anger, or boredom, contributing to weigh gain. Obesity is also associated with depression and low self-esteem (Montague, 2003).

There are numerous detrimental medical consequences of obesity: type two diabetes, hypertension, ischemic heart disease, stroke, asthma, gallstones, obstructive sleep apnea (OSA), depression, osteoarthritis of knees, hips, and feet, infertility, cancer of breasts, bowel, endometrium, and prostate, and gout. Obese women have 28 times
greater risk of developing Type 2 Diabetes than non-obese women with a BMI lower than 25 (Lawrence and Kopleman, 2004). Type 2 Diabetes exists because of obesity and with even modest weight loss, type 2 diabetes disappears. There are more than 14 million cases of Type 2 Diabetes in the United States and most are due to obesity. At a BMI of 25, one’s risk of developing Type 2 Diabetes is five times greater and at a BMI of over 30, one’s risk is thirty-five times greater than a non-obese person with a BMI lower than 25 (Dixon and O’Brien, 2002).

Cardiovascular disease results from obesity in that the excessive fat increases the body’s demand for oxygen. This high demand for oxygen via blood increases cardiac output. Ventricular hypertrophy occurs as a physiological adaptation by the ventricle in response to stress in an increased volume load. This occurs in order to maintain normal volume, despite an overload in demand. Ventricular hypertrophy occurs as a normal response during exercise to increase blood flow due to an increase in oxygen demand. However, chronic ventricular hypertrophy associated with obesity can lead to inefficiency and cause leading to diastolic (pressure while heart rests between beats) and systolic (pressure while heart pumps blood) dysfunction. This causes a decrease in function of the heart and possibly heart failure (Dixon and O’Brien, 2002).

Respiratory diseases are also common in the obese population. Obstructive Sleep Apnea (OSA) occurs with half of all obese patients. Breathing is hindered by increased fat deposits in the abdominal and chest walls, leading to periods of apnea and oxygen destruction (Lawrence and Kopelman, 2004). OSA occurs mainly with central adiposity in the gut, but can also occur in other forms of obesity. OSA can lead to daytime drowsiness and cognitive dysfunction. Asthma is common in obese patients, especially
obese children. 30% of all asthma cases are due to obesity. In children, there is a strongly positive correlation between the severity of overweight and the severity of asthma (Dixon and O’Brien, 2002).

Obesity can also affect pregnant women and fertility. Obese and overweight women face increased risks and costs in pregnancy. Hypertension, preeclampsia, late fetal death, and gestational diabetes are common complications. Most obese patient deliveries occur via cesarean section as well. The infants of these women also face increased risk of growth abnormalities and neural tube defects (Dixon and O’Brien, 2002). Polycystic Ovary Syndrome (PCOS) is an endocrine abnormality that causes amenorrhea and infertility. 50% of these cases are found in obese or overweight women. Severity of PCOS is directly correlated with the degree of obesity and a weight loss of 5% can ease the severity of the disease (Lawrence and Kopelman, 2004).

Obesity is associated with a significant increase of one’s chances of developing cancer. However, evidence can link cancer and obesity, but cannot prove that cancer would not develop in the absence of obesity (Lawrence and Kopelman, 2004). The changes that occur to the metabolic and endocrine systems in obesity can alter the regulation of cell processes of growth, differentiation, and apoptosis. Cancer of the breasts, endometrium, colon, and renal are common in obese patients (Lawrence and Kopelman, 2004).

This paper reviews the genetic and environmental contributions in developing and maintaining obesity, as well as the physiological functioning that defends body weight. The hypothalamic regions involved in body weight are discussed in conjunction with the associated neuropeptides. The anabolic pathways that stimulate food intake and a
decrease in energy expenditure include leptin, neuropeptide Y (NPY), and ghrelin. The catabolic pathways that decrease food intake and increase energy expenditure include cholecystokinin (CCK) and melanocortins. The interaction of these two pathways in the hypothalamus creates a negative feedback loop which defends an individual’s current body weight. This paper reviews the current understanding of the homeostatic mechanisms of body weight.

**Genetics**

Research shows that obesity has a heritability of 70-85% (Bouchard *et al*, 1998), which is greater/equal to height and other disorders that are considered to have a genetic basis (Friedman, 2002). The genes that would effect weight regulation are genes with encoding proteins and are thought to be numerous due to the complexities of body weight homeostasis (Loos *et al*, 2005). BMI correlations are higher between monozygotic twins (74%) than dizygotic twins (32%), regardless of shared environment (Barsh *et al*, 2000). Genes are responsible for variabilities in resting metabolic rate, weight gain in response to excess calories, and body fat distribution (Bouchard, 1994).

The single genes that produce obesity are rare and are called susceptibility genes (Perusse *et al*, 2001) and at least five single-gene defects are known (Barone *et al*, 1994). These rare genes involve leptin deficiency, defects in the leptin receptor, and defects in the processing of pro-opiomelancortin, pro-convertase 1, TSH-β, and PPAR-γ. These genes occur in a very small portion of the population, but are very powerful. The most common single gene defects involve the melanocortin receptor system (Perusse *et al*, 2001), especially MC4R (Lee *et al*, 2004). 5% of all childhood obesity can be attributed to MC4R genetic mutations (Friedman, 2004). For leptin mutations and defects, leptin
injections can cure obesity (Berthoud, 2004). A few specific genes involved in weight regulation are known. The beta-2 adrenergic receptor (ADR) gene encodes a 413 amino-acid protein which has a role in regulating energy balance by mediating glycogen breakdown and lipid mobilization (Loos et al, 2005).

A study with monozygotic male twins with no family history of obesity, hyperlipidemia (an increase of lipids, e.g. Cholesterol, in the blood stream), or diabetes showed similar body responses to overfeeding. The subjects ate an excess of 1,000kcal each day, six days a week, for 100 days. Researchers found at least three times more variance in weight and fat mass between pairs of twins than within pairs of twins. The different genetic makeup responded differently in gaining and distributing of fat mass. In abdominal visceral fat, there was six times more variance between pairs than within pairs. This study showed that different genetic dispositions respond differently to overfeeding; some individuals are more likely to gain weight than others and individuals gain weight in different areas. Weight responses are most similar within similar genetics than among individuals of different genetic backgrounds (Loos and Rankinen, 2005).

A similar study examined 14 pairs of female monozygotic twins whose caloric intake was restricted for four weeks. The individuals consumed a low-calorie diet of 380kcal/day. On average, the subjects lost 8.8kg of body weight and 6.5kg of body fat during the four weeks. However, there was 12.8 times more variability of body weight changes between genetic pairs than within and the variability in body fat loss was even greater. This study shows that certain genetic dispositions loose weight more easily and individuals with the same genetic makeup will respond similarly to caloric deficits (Loos and Rankinen, 2005). Both the overfeeding study and the caloric restriction study show
that the more genetically similar the individual body types are, the more similarly the individuals will respond to the ease of weight and fat gain, ease of weight and fat loss, and distribution of fat mass. However, the genes involved in body weight regulation are numerous and complex since homeostatic mechanisms, distribution of nutrients, adipogenesis, and rates of metabolism are complex genetic compositions (Loos and Rankinen, 2005).

A review of more than 10,000 individuals examined the correlation between BMI scores for monozygotic and dyzygotic twins and between biological parent-child environment and adoptive parent-child environment. The correlation of BMI between monozygotic twins was 0.74 and the correlation between dyzygotic twins was 0.32. This corresponds to an estimated genetic heritability of body weight of 50-90%. The BMI correlation between biological parent-child was 0.19 and the correlation between adoptive parent-child was 0.06 (Barsh et al., 2000). This study supports the role of genetics in obesity, in that more genetically similar individuals share more similar BMI scores.

The “thrifty gene” hypothesis explains the genetic influence of obesity from an evolutionary perspective. During evolution, food resources were scarce and significant physical energy was expended to find fuel. Therefore, the body adapted to store all available calories, since the time of the next fuel repletion could be lengthy. The genes which developed in response to the environment allowed for high caloric meals and efficient use of calories. Energy was stored in the form of body fat so that the individual could use the energy store in a time of food depletion. The body worked to ensure that enough food was ingested to provide for basic energy needs like growth, movement, and
reproduction. The development of obesity was very rare because these high caloric meals were sporadic and large amounts of energy were needed to obtain these meals (Berthoud, 2004).

Research has also shown that genes can affect an individual’s response to the environment, as well as behavioral affinities and preferences. Networks of genes can influence hunger and meal size, frequency of meals, amounts of carbohydrates, fats, and proteins consumed, and response to social context of eating, and time of day of eating (De Castro, 1999). Similar genes cause similar body type responses to energy surpluses and deficits and the distribution of fat mass. The basic understanding of obesity is that genes predispose an individual to develop obesity, but environmental influences are necessary in expressing the phenotype (Loos et al, 2005).

**Environment**

Environmental factors are necessary in developing obesity. Since obesity did not become a prevalent medical issue until the last thirty years and the drastic rise in its incidence, it is more likely that our environment has led to these changes more than our genetics. The “obesity-promoting environment” is necessary to show the phenotype. Evidence of this can be seen when individuals move from “restrictive environments,” environments in which food is not readily available, to “obesigenic environments,” environments that have high access to high-caloric foods, they gain significant amounts of body weight and body fat. However, those with the greatest genetic predispositions will gain the most weight, whereas some individuals are more resistant to gaining weight, possibly due to higher metabolic rates (Loos and Rankinen, 2005).
The obesigenic environment is also called the “toxic environment.” This type of environment is one that high caloric diets are easily accessible and a sedentary lifestyle is promoted (Colditz et al, 1996). Fast food restaurants, buffets, mini-markets in gas stations, fast food and soft drink contracts in schools, and advertisement of cheap, dense foods all contribute to the availability of high-fat foods. This environment perpetuates obesity and is still expanding; therefore the rise of obesity prevalence is on a steep increase (Foreyt and Goodrick, 1995).

Studies have shown that a sedentary lifestyle and a high-fat diet are the key predictors in developing and maintaining obesity. Individuals who ingest a high-fat diet paired with physical inactivity gain significantly more weight than do individuals who ingest high-carbohydrate diets paired with physical inactivity. The amount of fat intake is the main cause of obesity, not just a high-calorie diet alone. This is due to the high palatability of fat as compared to other types of food (Bell et al, 2001).

One study examined overfeeding in rodent pups. The rodent litter was reduced from 10-14 pups per litter to 3 pups per litter in order to increase access in postnatal feeding. During the postnatal period (before weaning), the overfed pups gained 10% more body weight than the controls who were in a normal sized litter. They also developed hyperglycemia and insulin resistance. The increase of body weight included two times more body fat and increased plasma leptin levels compared to the controls. Increases in NPY and AgRP mRNA in the ARH were responsible for maintaining the obesity after the postnatal period. This is likely due to alterations in the hypothalamic neuropeptide activity created by early onset obesity (Glayas et al, 2005). This study shows that overfeeding is a main source of obesity and overweight. This study also
demonstrates that early onset obesity has long-term consequences. Early onset obesity usually continues into adulthood obesity due to neuropeptide changes and metabolic dysfunction.

Our environment promotes a high-calorie diet and discourages physical activity. Patterns have changed in what we eat, where we eat, food processing and production, and eating options. Patterns in the way we move and communicate have also changed, where travel and transportation is convenient and technology allows us to perform tasks with minimal amounts of energy exerted. These pattern changes have created an imbalance on energy which promotes, develops, and perpetuates obesity and overweight. The total amount of calories per day has increased for all age groups, gender, race, socioeconomic status. The availability of exercise resources can promote or discourage physical activity. Minority, low educated groups are the biggest disadvantage for exercise resources (Duffey et al, 2005).

Without influence from the environment, obesity would not be a serious medical problem. The body cannot defend its weight against chronic ingestion of high fat food, especially in the absence of physical activity. Our environment contributes to the development and perpetuation of obese and overweight. High fat intake is a key predictor of obesity, not just high caloric intake.

**Hypothalamus and Neuropeptides**

Daily caloric intake is moderated by the interaction between the gastrointestinal tract and the hypothalamus. The hypothalamus contains a complex network of nuclei and peptides, which receive information afferently from the periphery and in turn modify efferent biological processes (Chen et al, 2004). The two most important food regulating
regions in the hypothalamus are the arcuate nucleus (ARC) and the paraventricular nucleus (PVN). Both are located near the third ventricle in the brain (Chen et al., 2004). Other hypothalamic regions important in weight regulation are the ventromedial hypothalamus (VMH), the dorsomedial hypothalamus (DMH), and the lateral hypothalamus (LH) (Bing et al., 2001).

The ARC acts as a controlling center for insulin, leptin, ghrelin, NPY, and α-MSH (Chen et al., 2004). This network of neuropeptides regulates signals for chemical release. This allows a balance of the anabolic and catabolic pathways. The anabolic pathways stimulate food intake (orexigenic) and decrease energy expenditure, resulting in weight gain. Catabolic pathways suppress food intake (anorexigenic) and increase energy expenditure, resulting in weight loss (Benedict et al., 2004). The ARC also has connections with the PVN, DMH, and VMH. Endocrine and duodenal signals meet between hypothalamic nuclei and the caudal brainstem.

The PVN acts as an integrating system, where many neural pathways that modify energy balance diverge. The PVN receives metabolic signals and then initiates appropriate responses in order to maintain body weight homeostasis via food intake or energy expenditure (Glayas et al., 2005). It contains NPY, α-MSH, serotonin (5HT), galanin, nonadrenaline, and opioid peptides. The PVN is very sensitive to the effects that the neurotransmitters have on weight regulation (Bing et al., 2001). The PVN can activate the hypothalamic-pituitary adrenal axis and the anterior and posterior pituitary signal (HPA axis), creating an afferent feedback loop that regulates weight balance (Chen et al., 2004).
Another hypothalamic area involved in energy regulation is the ventromedial hypothalamus (VMH). It is one of the largest nuclei in the hypothalamus. There is a large amount of leptin receptors present, suggesting that the VMH is an important leptin target for stimulating food intake and decreasing energy expenditure. Stimulation of the VMH inhibits food intake and lesioning the VMH results in weight gain (Bing et al., 2001).

The DMH has an abundance of direct connections with the PVN, LH, and brainstem. This suggests that the DMH has a powerful role in influencing other hypothalamic regions. Research has suggested the DMH and the PVN work together to initiate and maintain food intake. There is a large number of neuropeptide receptors found the DMH. Therefore the DMH has a role in influencing other hypothalamic regions via its connections and abundance of neuropeptides (Bing et al., 2001). The DMH is also the nuclei that generates a response to hypothalamic stress and stimulates the HPA axis via its PVN projections. The DMH also activates the sympathetic nervous system. Therefore, the DMH is an integration center that induces responses through its projections to other hypothalamic nuclei, especially in times of perturbations from homeostasis (Bailey et al., 2003).

Stimulation of the LH increases food intake and lesions cause a decrease in food intake, resulting in weight loss. The LH has a large number and variety of neurons that express orexins and MCH, both which stimulate food intake. NPY receptors are also abundant, which also stimulate food intake (Bing et al., 2001).

Anabolic pathways in the hypothalamus stimulate food intake and decrease energy expenditure and metabolism, causing weight gain. The neuropeptides that exert
this orexigenic influence include leptin, NPY, and ghrelin. Catabolic pathways in the hypothalamus inhibit food intake and stimulate energy expenditure and metabolism, causing weight loss. CCK and melanocortins are neuropeptides that exerts these anorexic effects. The interactions between the anabolic and catabolic neuropeptides maintain homeostasis of body weight.

Leptin is thought to be the most important chemical in regulating body weight. Leptin is a hormone that is secreted by white adipose tissue and functions as an afferent signal in the regulation of body weight. Leptin informs the brain of how much energy is stored in the form of fat mass and modifies the hypothalamic pathways and brainstem activity to maintain weight homeostasis in the body. Leptin is a long-term signal that balances energy expenditure with energy intake, resulting in the amount of long-term fat/energy storage. However, leptin can also interact with short-term signals to modify daily meal patterns (Friedman, 2002). Leptin acts mainly on the hypothalamus and receptors that are found in the arcuate nucleus (ARC), ventromedial hypothalamus, dorsomedial hypothalamus (DMH), and lateral hypothalamus (LH), all of which have a role in body weight regulation. The leptin receptor is a member of the cytokine family of receptors (Friedman, 2002) and effects homeostasis through the LRb long receptor (Ahima, 2005). Leptin enters the central nervous system (CNS) across the blood brain barrier by means of a saturable transport mechanism and binds to the long form of the leptin receptor (Ob Rb) in the ARC (Banks et al, 1996). The exact process is not fully understood (Ahima and Osei, 2004).

When levels of leptin are low, the body enacts a “starvation response” in which energy expenditure and body temperature is decreased (Friedman, 2002) and appetite is
Leptin inhibits NPY and AGRP whose role is to increase food intake and decreases metabolism. Leptin also enhances POMC whose role is to decrease food intake (Friedman, 2004). In a normal individual, the amount of circulating leptin is directly proportional to the amount of body fat; the more fat mass, the more leptin is circulating to inform the body that there are enough fat stores. This is part of the negative feedback loop that helps maintain energy balance. Individuals produce specific amounts of leptin in order to maintain a set-point of body weight (Friedman, 2002).

Leptin levels are increased in obesity and decreased during periods of fasting. The majority of obese individuals have increased levels of circulating leptin, which suggests an insensitivity or resistance to leptin compared to normal weight subjects. Reasons for the resistance of leptin include defects in the transportation pathway, defects in leptin signaling, inefficient uptake across the blood brain barrier, environmental medication of sensitivity, or a combination of all factors (Friedman, 2002). CSF levels of leptin are lower in obese individuals than in normal weight individuals, supporting the idea that obesity is a result of inefficient uptake across the blood brain barrier (Ahima, 2005). Leptin sensitivity can be altered by environmental factors through a high lipid diet which modifies hypothalamus signaling or modification of reward pathways across the hypothalamic leptin pathways (Friedman, 2004).

The ob/ob mouse is obese due to a mutation in the leptin gene. Therefore, the brain never receives the signal that there are enough fat stores so the mouse perceives a state of starvation. The mice are continually stimulated to eat and to decrease energy expenditure. In this case, direct injections of leptin cure obesity (Friedman, 2002).
Whereas, the db/db mouse has an inactivation of the leptin receptor (Campfield et al, 1995) and the fa/fa mouse has a mutated leptin receptor (Collum et al, 1996).

Leptin can affect, and be affected, by many systems such as homeostatic, neuroendocrine, immune, reproductive and cardiovascular systems (Ahima, 2005). Leptin interacts with insulin at the post-receptor level. Insulin inhibits food intake in normal body weight individuals (Collum et al, 1996). Seratonin (5HT) can affect the hypothalamic pathways, as well as other hormones (Friedman, 2004). The rate of glucose uptake in adipose tissue can change levels in circulating leptin (Born et al, 2000).

Leptin also might be involved with the immune system and sufficient amounts of leptin are needed for the onset of puberty. This could explain why anorexic girls do not have a menstrual cycle; their levels of leptin are too low due to extremely low amounts of fat mass (Friedman, 2002).

Neuropeptide Y (NPY) is one of the most abundant and distributed neuropeptides in the brain (Gehlert, 1999), and possibly the most potent appetite stimulant (Cai et al, 2004). The 36 amino-acid peptide is part of the pancreatic polypeptide family. NPY is involved with energy homeostasis by stimulating feeding, decreasing energy expenditure, and increasing storage of energy as fat. It has been found that NPY stimulates mostly the intake of carbohydrates, but also stimulated moderate fat intake as well (Gehlert, 1999). Blood pressure, memory retention, and circadian rhythms can also be affected by levels of NPY since it is widely distributed throughout the brain and effects other process other than body weight regulation (Herzog, 2003). NPY levels are high before eating and are also elevated in obese individuals. NPY also increases the size of the meal, but not the frequency of meals (Gehlert, 1999). The storage of energy as adipose tissue is increased
via an endocrine and metabolic response that NPY triggers. When metabolism is decreased, more energy is stored as fat. NPY stimulates the “starvation response” so that energy is stored as adipose tissue and extraneous energy expenditure is decreased. NPY is found in the arcuate nucleus (ARC) of the hypothalamus and also has concentrations in the cerebral cortex, brainstem, hippocampus, and limbic regions (Gehlert, 1999). Projections of NPY from the hypothalamus lead into the PVN and DMH, which are also involved in energy regulation (Cai et al, 2004).

Injections of NPY lead to an increase in food intake and chronic injections lead to obesity (Herzog, 2003). This is because the body will defend its weight against brief increases in food intake/decreases in energy expenditure, but cannot defend repeated intake. Therefore, without defense against chronic insults to the homeostatic system, obesity will result with chronic NPY injections. An NPY antagonist reduces food intake (Gehlert, 1999). Altered expression of hypothalamic NPY is important in developing obesity (Herzog, 2003). Many obese individuals have cravings to eat even when they are not hungry, signaling a altered expression of NPY. The desire to eat must overcome the feeling of satiety in order to develop obesity. Research has also shown that NPY surges are present during periods of stress (Gehlert, 1999). This may explain why many individuals eat in response to stress.

There are six NPY receptors known: Y1, Y2, Y3, Y4, Y5, and Y6. Erickson had the first NPY knockout model in 1996, replacing NPY with lacZ gene. No gross abnormalities were found. The NPY gene in mice did not reduce body weight, food intake, or adiposity (Herzog, 2003). However, Y1 receptor knockout models have shown conflicting results: some research shows no changes in body weight or food intake when
the Y1 receptor is disabled (Herzog, 2003) and some research shows increased body weight and fat mass with small caloric intake in the Y1 receptor knockout model (Gehlert, 1999). Therefore, the exact role of Y1 is not fully understood due to unreliable results. The Y2 receptor is pre-synaptically expressed and has a role in regulating synthesis and release of NPY and other neurotransmitters in energy homeostasis. The Y4 receptor is the least understood receptor, having little research conducted on its role. Researchers do know that it is found mostly in peripheral tissue, the PVN, and brainstem. The Y5 receptor has been called the “feeding receptor.” Y5 knockout models show that mice develop within a normal body weight when they are young, but develop late obesity by increasing food intake with an inactive Y5 receptor (Herzog, 2003). The Y5 receptor is expressed in the amygdala, hippocampus, PVN, and ARC (Cai et al, 2004).

Researchers believe that the Y1 and Y5 receptors are the most important role in feeding (Gehlert, 1999). The knockout models have also shown that a removal of one NPY receptor can cause other systems and neuropeptides, especially AgRP (Cai et al, 2004), to compensate for the dysfunction of NPY in maintaining energy homeostasis (Herzog, 2003).

Ghrelin is an anabolic neuropeptide which stimulates feeding and decreases energy (Cai et al, 2004). This neuropeptide was first found in the stomach, but has now been found to be located in the hypothalamic areas of the ARC, PVN, LHA, VHM, and DL (Chen et al, 2005). There is special emphasis on the role of ghrelin in the ARC (Beck et al, 2004). Therefore it is both a peripheral and central nervous system peptide. Ghrelin is a natural ligand of the growth hormone secretagogue (GHSR), but the growth stimulation effect is independent of the energy homeostasis effect (Beck et al, 2004).
Circulating ghrelin from the gastrointestinal tract can stimulate the hypothalamic neural circuitry (Masaki et al., 2005). Ghrelin receptors are co-localized with Leptin receptors in the ARC, suggesting an interaction between leptin and ghrelin for the control of energy regulation (Beck et al., 2004). Ghrelin levels are high after fasting and before eating when there is an absence of food in the gut and decreased after eating when there is a food store. Administration of ghrelin causes increased fat mass and body weight through its stimulatory effects on food intake and inhibitory effects on energy expenditure, including decreased metabolic rate (Chen et al., 2005).

A study with obese Zucker rats found that levels of Ghrelin change with age. At two months old, levels of Ghrelin were significantly lower in the obese rats than in the lean rats. In the obese rats, the intake of ghrelin was inversely related to body fat. At two months old, the obese rats weighed 50% more than the lean rats. However, at six months old, Ghrelin levels of the obese rats had evened out with the levels in the lean rats. The body weight of the obese rats at six months old was not significantly different from the body weight of the obese rats at two months old. The two month old obese rats had lower levels of ghrelin than the six month old lean rats. The lean rats had 2.6% fat mass, where the obese rats had 12.1% fat mass. Rats can have low levels of Ghrelin and high levels of body fat mass (Beck et al., 2004). These results also show that the ghrelin functioning is down-regulated in obese rats and body composition is more important than body weight.

Ghrelin also has roles in insulin secretion, adipogenesis, and lipid metabolism. Ghrelin stimulates differentiation of preadipocytes in adipose tissue, which transforms an undifferentiated cell into an adipose cell permanently, and antagonizes lipolysis, or
prevents the breakdown of adipose cells. Higher levels of Ghrelin are associated with low levels of thermogenesis. Uncoupling proteins (UCPs) are found in Ghrelin. UCP’s are located on the inner mitochondrial membrane, which is the energy source of the cell. UCP’s are free fatty acid transporters which allows protons to reenter the mitochondria. These protons dissipate energy from the mitochondria as heat, thermogenesis. Brown adipose tissue (BAT) contains mitochondria and is characterized by the presence of UCP’s. UCP1 regulates energy expenditure. This occurs because energy expenditure in BAT is controlled by the sympathetic nervous system. Ghrelin, when central administered, suppresses BAT sympathetic nervous system activity. This finding suggests that Ghrelin inhibits energy expenditure via suppression of BAT activity. When the protons are not allowed to reenter the mitochondria, they cannot dissipate energy. The UCP2 function is unclear, but maybe involved in limiting free radical entry in cells (Masaki et al, 2004).

Melanocortins have been receiving increasing attention for their role in weight regulation. Alpha-melanocyte stimulating hormone is a 13 amino acid peptide hormone, cleaved from pro-opiomelanocortin (POMC). The effects of $\alpha$-MSH are mediated through a G-protein (Baik et al, 2005). The melancortin receptors have five subtypes: MC1-R, MC2-R, MC3-R, MC4-R, and MC5-R. MC4-R is found to have the most important role in body weight regulation (Benedict et al, 2004). Stimulation of MC4-R causes an increase in energy expenditure and a decrease in food intake via $\alpha$-MSH mediation. It was also found that genetic mutations of MC4-R caused obesity in mice. When $\alpha$-MSH was replaced with Gln or Lys, there was a significant suppression of food intake. (Baik et al, 2005). MC4-R agonists are therefore being studied as a therapy for
obesity. Research has also shown that genetic mutations of MC3-R in mice cause
increased fat mass and a decrease lean mass without an increase in food intake. Research
has concluded that the suppression of melanocortin food regulation is related to the
peptide structures, which are essential for the physiological functioning of the
melanocortin receptors (Baik et al, 2005).

Cholecystokinin (CCK) has a wide distribution and is one of the most abundant
neuropeptides in the central nervous system (CNS) (Moran and Schwartz, 1994). When
administered to the periphery, CCK decreases food intake and stimulates behavioral
satiety (Bi and Moran, 2002). Rats injected with CCK stop eating and rest. This suggests
a role in endogenous food satiety and meal size. CCK is found both in the
gastrointestinal tract (GI) and the brain. In the periphery, CCK is released from the
duodenum and jejunum (intestines) in response to ingested nutrients and can also cause
pancreatic secretion, gallbladder contraction, intestinal motility, and suppression of
gastric emptying. CCK also reduces meal size and initiates satiety behaviors. These
peripheral actions depend on the vagus nerve, which has CCK receptors that are
connected to afferent fibers. CCK centrally inhibits food intake. In rats with
dysfunctional CCK, meal size is doubled but meal frequency is not significantly lowered
to prevent obesity. This inability to compensate for dysfunctional CCK supports an
important role for CCK-A receptors in feeding regulation (Bi and Moran, 2002).

There are two receptor subtypes for CCK: CCK-A and CCK-B, which both act
through G-proteins. CCK-A is found in alimentary tissues and CCK-B is found the brain.
Research has suggested that CCK-A is the more important receptor of the two. The
distribution of CCK-A is species specific, meaning, each animal has different levels of
CCK-A throughout different parts of the brain. The inhibition of food intake in the periphery depends on the activation of CCK-A receptors of both exogenously administered and endogenously released. Therefore, the hormones released from the gut and the neuropeptides from the hypothalamus interact to suppress ingestion in the gut (Bi and Moran, 2002).

Discussion

There are two types of obesity: genetic and dietary. The homeostatic regulation of obesity refers to the dietary form of obesity (Hirvonen and Keesey, 1997). The homeostatic control over our body weight is extremely accurate (Berthoud, 2004), with about 99.5% constancy (Friedman, 2004). Meaning, our body weight is remarkably consistent over many years, whether that weight is normal or overweight. Homeostatic regulation includes the mechanisms that receive feedback from the controlled area (body fat) and creates an error signal from the perturbation in present balance (food intake versus energy expenditure) (Berthoud, 2004). Von Helmholtz described the First Laws of Thermodynamics, which states that the amount of energy in a closed system must remain constant. In the sense of energy balance in humans, to maintain constant weight, the amount of food ingested and the amount of energy expenditure must match. An imbalance will result in either weight gain or weight loss (Friedman, 2004). The homestatic regulation is much like the regulation of body temperature or a thermostat. Obesity is generally viewed as a behavioral problem, but behavioral therapy does not alleviate obesity, supporting the idea that obesity is physiological in nature. Therefore, a state of obesity could be the natural physiological state for certain individuals (Hiroven and Keesey, 1997).
Individual body weight varies approximately 0.5% over six to ten weeks, which is very stable. Research has also shown that weight fluctuations over longer periods of time are just as stable. This tight regulation suggests a physiological defense of weight. Rats displaced from normal body weight are quick to restore normal weight. If an individual’s weight decreases, anabolic neuropeptides like AGRP, NPY, Ghrelin, MCH, and orexins are stimulated. In one study, when calories were reduced by 14.9%, resting metabolism declined by 24.6% (Hiroven and Keesey, 1997). Resting metabolism refers to the processes that simply keep the body functioning like the metabolism of food, transport of sodium, potassium, and ions across cell membranes, the repair of DNA, synthesis of proteins, pumping the heart, functioning of the brain, liver, and kidneys. This requires that a mix of fuels be oxidized (Esposito-Del Puente et al, 1990). If an individual’s body weight increases, catabolic neuropeptides are stimulated. Max Kleiber created an equation for daily resting metabolism in relation to body weight: kcal/d=\( k \times BW_{kg}^{0.75} \). By this standard, energy expenditure increases by \( \frac{3}{4} \) of body mass (kg) as body weight increases. Meaning, as an individual gains body weight, the body will increase energy expenditure proportionally, in order to defend the physiological body weight. This equation accounts for resting metabolism rates in different-sized animals of the same species. Heavier rats metabolize energy at a higher rate than leaner rats. When obese rats lost weight, their metabolism also dropped. This suggests that individuals metabolize at rates suitable to maintain their current body weight, even if the current body weight is obese. Lesions of the LH create body weight maintenance at below average body weight (Hiroven and Keesey, 1997).
The negative feedback loop in maintaining body weight has four aspects. The control center (brain) receives information about the state of adiposity. The information is transduced into a signal, in the form of neuropeptides discussed earlier, that activates pathways that either stimulate or suppress food intake to restore energy balance. The signals received by the brain are part of the afferent loop. These signals keep the brain informed with the current environment via sense organs and keeps the brain alert to body functioning through neural, nutrient, and hormonal signals. The brain’s response is either to stimulate or suppress the motor systems and adjust the hormones for food intake or food suppression. The controlled system performs actions and consists of the digestive tract (ingests, digests, and absorbs food), metabolic systems in the liver, muscle, and kidney (transform nutrients), and adipose tissue (stores and releases fatty acids) (Bray, 2002).

Defending weight changes are easily accomplished with initial changes. Rats with high fat diets defended lean body weight by increasing metabolism. The initial weight gain with increased caloric diets were small. These short-term weight gains are easily reversible. However, chronic high fat diets which produce obesity can be seemingly irreversible. Weigh gain includes an increase of adipose cell size by an average of 61% and an increase of adipocyte cell number by 48% (Hirvonen and Keesey, 1997). The body can defend lower level obesity but not higher level obesity (Berthoud, 2004).

There are long-term and short-term signals to maintaining weight. Long term afferent signals include leptin and insulin which control overall body weight over months. Short term afferent signals regulate individual meals and derive from the gut
When leptin was discovered, it was believed to be the feedback signal for body fat (Berthoud, 2004). Without leptin, individuals do not have a signal telling the brain how much fat there is, so the body continues to build up fat stores. Research has suggested that leptin acts as a starvation signal, not a adiposity signal (Berthoud, 2004).

In opposition to the homeostatic system is the nonhomeostatic system which consists of an abundance of food cues in the environment, easy availability of foods that are palatable, high calorie, and socially facilitated. The homeostatic regulation of body weight becomes dysfunctional or impaired in response to this nonhomeostatic system. Sometimes initiation and termination of ingestion is stimulated by cognitive and environmental factors which override neuropeptide signals. Palatability is the most important nonhomeostatic cue which stimulates food intake. In an experiment of preference, when give the choice of protein, carbohydrates or fats, rats ingested significantly more fats (Berthoud, 2004). Enhancing the flavor of food can increase food intake in satiated rats, which can lead to obesity. Bitter and sweet tastes are recognized at birth in the brainstem and rewarding tastes of specific stimuli are learned later. The social context and conventional meal times also increase food intake. Our bodies are designed for energy depletions (thrifty gene hypothesis), not energy excesses, which set us up for obesity (Berthoud, 2004).

Cognitive decisions can overwrite neuropeptide and hormonal signals. The cortex and limbic systems can overpower the hypothalamic signals, just as the hypothalamic signals can overpower the cognitive signals in starvation. The metabolic and nonmetabolic signals converge in areas like the nucleus of acumbens, amygdala, brainstem, prefrontal cortex, and hypothalamus (Berthoud, 2004).
Treatment Options and Directions

The first line therapy for obesity is the least risky. This treatment option includes diet, exercise, and behavior modification and is generally used for individuals with an BMI of 25-30 (National Institutes of Health, 2000). The diet should contain less than 800 kcal/day Bethesda, 2000). Diets rich in vegetables, fruit, an especially dairy can assist in weight loss (Allard et al, 2004). Research has shown that calcium levels negatively correlated with obesity (Davies et al, 2000). Also, infants who breastfed for more than three months have significantly reduced risk of developing obesity due to the nutrients found in breast milk (Landsberg et al, 1993). Physical activity is recommended three to four times a week for thirty to sixty minutes and can account up to 2-3% weight loss without dieting. Behavior therapy is centered on learning principles such as reinforcement. A combination of all three (diet, exercise, and behavioral modification) is the most effective treatment for first line therapy. However, these therapies are unsuccessful for morbidly obese individuals and regaining weight is very common (Bethesda, 2000).

Pharmacotherapy is the second line therapy for obesity, involving increased risks and more intense measures for individuals with a BMI of 27-30 (National Institutes of Health, 2000). There are two drugs approved by the Food and Drug Administration (FDA) for the treatment of obesity: Orlistat and Subutramine. Orlistat inhibits pancreatic lipase, resulting in a decrease of the absorption of dietary fat by 30%. There is a 4% greater weight loss for Orlistat as opposed to the placebo trials. Subjects have lost up to 150-180 kcal a day by taking Orlistat. However, this method still requires a low calorie diet (Andersen et al, 1998). Orlistat can be used by individuals with Type 2 Diabetes in
order to reduce elevated levels of hemoglobin A1C and manage blood glucose levels. Side effects of Orlistat can include a disruption in vitamin absorption, gastrointestinal upset, oily spotting, flatus with discharge, fecal urgency, and oily or soft stool (Glazer, 2001). Subutramine acts centrally to inhibit the reuptake of norepinephrine, dopamine, and serotonin. Research shows significantly greater weight loss with subutramine than with the placebo (Aronne, 2001). Also, there was significantly greater maintained weight loss after a year than the placebo. Side effects can include increased heart rate and blood pressure, reduced lipids and insulin levels. Subutramine should not be taken in conjunction with MAOIs, SSRIs, or any type of antidepressants (Glazer, 2001).

The third line of therapies involves surgery, with increased risks and invasive procedures. This therapy is reserved for those who are morbidly obese (BMI of 30 and above) and do not respond to the other therapies (National Institutes of Health, 2000). Two surgical therapies are common in the treatment of obesity: gastric bypass (GB) and vertical banded gastroplasty (VBG). GB creates a small gastric pouch at the end of the esophagus in order to limit food intake. The stomach and duodenum are bypassed. The average weight loss in this procedure is 30% in an 18 month period. This treatment is good for individuals prone to consuming more sweet/sugary foods because it releases an unpleasant feeling after the ingestion of refined carbohydrates. VBG creates a small pouch in order to limit food intake but without altering any gastrointestinal parts (National Institutes of Health, 2000).

New research is focusing on Ciliary Neurotrophic Factor (CNTF), which is a protein that activates hypothalamic intracellular signaling pathways that regulate food intake and weight balance. It acts as a satiety signal that leads to a decline in food
consumption. rhvCNTF was genetically produced as a form of CNTF to be used as a weight loss drug. Twelve weeks of rhvCNTF intake had significantly greater weight loss than the placebo. This form of the drug is on the “fast track” of research from the FDA and will be used for life threatening obesity (Vastag, 2003).

There are a few additional research projects to create a new anti-obesity treatment. One type of research is searching for a new cannabinoid receptor (CB1) antagonist that will act as an appetite suppressant. This treatment was found to decrease body weight in obese mice but is still being researched (Arone et al, 2003). Also, α-lipoic acid (α-LA) has found to have anti-obesity effects by inhibiting hypothalamic AMPK, which is an enzyme that acts as an intracellular energy sensor that is activated when the energy store of a cell is low. α-LA decreases food intake and body weight and stimulates energy expenditure in rodents. Therefore, α-LA could be a possible obesity treatment in the future (Lee et al, 2004).

New research is also focusing on reversing adipogenesis. Adipogenesis is the cellular conversion when fibroblastic cells form preadipocytes, then form a multiocular adipocyte, then a mature (unilocular) adipocyte. Previous research has assumed that once a preadipocyte gathers lipids, the cell terminally forms a differentiated adipocyte that can only metabolize lipids. New research has suggested that mature adipocytes can dedifferentiate to proliferative-component cells. Pharmological treatments can possibly form a drug that makes mature cells regress back to an undifferentiated cell, which could make it possible to terminate the cell so that fat cannot be stored by those cells anymore. More research is necessary in understanding the exact mechanisms of adipogenesis (Antonio et al, 2005).
This paper reviewed the balance among influences in body weight, including genetics, environment, and hypothalamic neuropeptides. The body has homeostatic mechanisms that will defend its physiological weight, regardless whether that weight is normal or obese, presenting difficulties in weight loss. Genetics predispose an individual to obesity, but environment is necessary in order to express the phenotype. The environment in the United States promotes and perpetuates obesity in that high fat foods are readily accessible and physical exercise is discouraged by convenient technology. Anabolics and catabolic neuropeptides are balanced in the hypothalamus in order to maintain body weight. In conclusion, there are several lines of therapy, depending on the level of severity of obesity, including prevention.

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