Failures of Feedback: Rush Hour Along the Highway to Obesity

WAYNE GADE, JEAN GADE, MELISSA COLLINS, JESSICA SCHMIT, NICOLE SCHUPP

LEARNING OBJECTIVES

After reading the following article, the reader should be able to:

1. Define obesity, in terms of body mass index or BMI.
2. Describe the hormones and functions of the HPA system and non-HPA hormones.
3. List and describe the three primary ways that the hypothalamus helps regulate body weight.
4. Describe the molecular types and tissue of origin for leptin, insulin and cortisol.
5. List and describe four "entrance ramps" to the "highway to obesity."
6. Describe how leptin and insulin resistance are related to the development of obesity.
7. Describe "lipid buffering" and how it relates to ectopic fat deposition.
8. Describe how the dopamine "pleasure/reward system" is involved with such diverse behaviors as drug and alcohol abuse and overeating.
9. Discuss the impact of inheritance on an individual's tendency to become obese.
10. Identify analytes that are typically elevated by the metabolism of obesity versus analytes that are decreased or unchanged.

The Focus section seeks to publish relevant and timely continuing education for clinical laboratory practitioners. Section editors, topics, and authors are selected in advance to cover current areas of interest in each discipline. Readers can obtain continuing education credit (CE) through P.A.C.E.® by completing the continuing education registration form, recording answers to the examination, and mailing a photocopy of it with the appropriate fee to the address designated on the form. Suggestions for future Focus topics and authors, and manuscripts appropriate for CE credit are encouraged. Direct all inquiries to the Clin Lab Sci Editorial Office, Westminster Publishers, 315 Westminster Court, Brandon MS 39047. (601) 214-5028, (202) 315-5843 (fax). westminsterpublishers@comcast.net.

Clin Lab Sci 2010;23(1);39

***Wayne Gade**, PhD, MT(ASCP), **Associate Professor**, Clinical Lab Science Program, University of Illinois Springfield, Springfield, IL*

***Jean Gade**, MS, BS(RN), **Nurse Educator**, Lincoln Prairie Behavioral Health, Springfield, IL.*

***Melissa Collins**, MLS (ASCP), **Medical Lab Scientist**, Skokie Hospital, 9600 Gross Point Rd, Skokie, IL.*

***Jessica Schmit**, **Student**, Clinical Lab Science Program, University of Illinois Springfield, Springfield, IL.*

***Nicole Schupp**, MLS (ASCP), **Medical Lab Scientist**, Memorial Medical Center, Springfield, IL.*

***Address for Correspondence:** Wayne Gade, Clinical Laboratory Science & Chemistry Departments, HSB Rm 314, One University Place, Springfield, IL 62703, wgade1@uis.edu, 217-725-6384.*

Abstract

From hot dogs to Hashimoto's and inheritance to inactivity, many "entrance ramps" converge onto the "Highway to Obesity", each contributing caloric intake that exceeds expenditure. Initially, the hypothalamus regulates appetite and energy based on leptin feedback, until feedback failure increases appetite, and allows deposition of abdominal fat, metabolic dysregulation, and metabolic syndrome. Without feedback controls, progress toward obesity is unimpeded unless diet, exercise, and/or medications provide an exit ramp.

Introduction

The worldwide obesity epidemic extends well beyond the borders of the United States or North America.

Two-thirds of US adults are overweight and 67 million (32%) are obese.[1,2] The percentages of obese adults in the United States increased substantially from 1994 to 2007 as shown in Figure 1.[2] Over half of Germans are overweight.[3] Although the percentage of obese adults is lower in China and India, each country has twice as many obese people as the United States.[3] The obesity epidemic includes less developed countries, such as Mexico, where 70% are overweight, and Egypt, where 60% are overweight.[3]

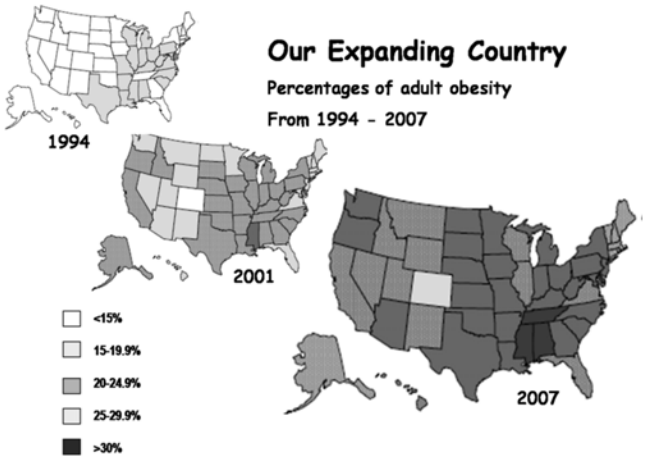


Figure 1: Changes in Percentage of Adult Obesity
The 1994 map shows that most states had adult obesity percentages below 15% and no states had percentages over 20%. By 2001, all states except Colorado had obesity percentages over 15%, and 28 states had more than 20%. In 2007, only Colorado had less than 20% obesity and three states had increased to more than 30% adult obesity. Modified with permission from CDC website on Obesity. (http://www.cdc.gov/nccdphp/dnpa/Obesity accessed 11/10/2008)

Obesity results from a positive energy balance (PEB) and is associated with type 2 diabetes mellitus (DM2); colon, endometrial, and breast cancer; renal, gall bladder, and liver diseases; polycystic ovarian syndrome, coagulation disorders, sleep apnea, stroke, osteoarthritis, gynecological problems, ocular diseases, and development of atherosclerosis and cardiovascular disease (CVD).[4-11]

Body mass index (BMI), mass (kg)/height2 (m) is commonly used to classify status: BMIs greater than 25 indicate overweight, over 30 is obese, and over 40 is considered extremely obese.[4,5,7,12] People with large lean muscle mass and minimal body fat could mistakenly qualify as obese. For example, Arnold Schwarzenegger in his Mr. Universe prime, had a BMI over 30.

Molecular physiology has significantly increased our understanding of the development of obesity, yet it offers an incomplete picture. We must also consider that many dietary choices represent conscious decisions to ignore internal signals of satiety, often in futile attempts to quiet noise from a stressed-out society.[6,13,14] Patients who are stressed and/or depressed may overeat because they find control and comfort in food. Children learn bad eating habits, while others overeat simply because they enjoy food. Advertising promotes economical "supersized" portions that offer large quantities of cheap calories and prolong the enjoyment of eating, but require us to ignore molecular signals of satiety. Overeating often represents addictive behavior, involving the dopamine pleasure-reward system similar to the basis of drug and alcohol addictions.[13,14] Figure 2 illustrates many of the "entrance ramps" for the "Highway to Obesity."

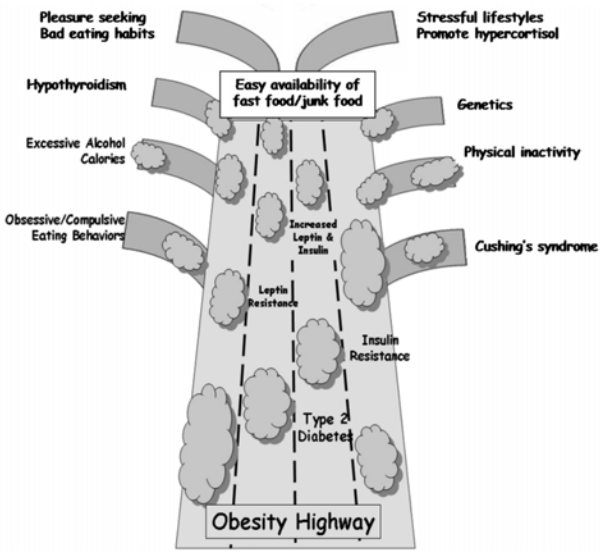


Figure 2: Multiple Entrance Ramps Along the Highway to Obesity
Many roads enter the obesity highway, each one delivering excessive calories or decreased caloric requirements, or both. The common characteristic is a chronic positive energy balance (PEB) that overwhelms metabolic and hormonal controls and eventually demands ectopic fat deposition. Development of leptin and insulin resistances leads inevitably to obesity if diet, exercise, and/or drugs cannot provide an exit ramp.

Genetics accounts for approximately half of the observed weight or BMI variation within a population, but the genetic contribution is polygenic and individual "obesity genes" typically make small contributions toward a person's BMI.[15,16] To date, most polymorphisms alter feedback mechanisms, and cause ineffective control of appetite and metabolism.[15,16] Regardless of the underlying cause, a consistent PEB precedes obesity and destroys delicate feedback systems. Simplistically, the body ignores signals intended to suppress overeating, and excess calories are deposited as abdominal fat, resulting in lipotoxicity, inflammation, CVD, and other diseases.[4,5,7] This review concentrates on hormonal and metabolic changes resulting in chronic overindulgence and obesity. The accompanying article focuses on metabolic syndrome and the toxic and destructive consequences of obesity.[17] Examples of clinical case data, including lipid profiles, glucose, and hormone levels will be presented in a future article.

Methods

A comprehensive list and description of methods used to investigate the complex molecular interactions leading to obesity is beyond the scope of this article. Molecular Diagnostics, by Buckingham and Flaws, offers an excellent "primer" of molecular techniques [18] and Tietz Fundamentals of Clinical Chemistry, edited by Burris and Ashford, provides an excellent background of clinical methodology.[11]

Expanding Our Search for Molecular Explanations

Adipocytes: Factories, Not Just Warehouses

Traditional endocrinology described the roles of insulin, glucagon, cortisol, epinephrine, thyroxin, and the hypothalamus-pituitary axis (HPA) in metabolism, but failed to adequately explain the development of obesity.[12] The hypothalamus, through the HPA directs three major functions associated with body weight and obesity:[4,5,12,19,20]

1. Control of metabolism (anabolic, catabolic, and thermogenesis).
2. Sensations of hunger or satiety and food preferences (such as comfort foods).
3. Control of physical activity (for energy use or conservation).

But what signals elicit the appropriate responses by the hypothalamus, allowing it to maintain normal metabolism and avoid weight gain? Complex input from sensory and neuronal circuits are balanced with hormonal feedback to provide a remarkably effective homeostasis mechanism. When signals are ignored, as occurs with insulin resistance in DM2, homeostasis is destroyed.[10,12,19,20] Questions concerning weight gain, appetite, and the frustrations of dieting remained unanswerable without additional factors. The unexpected source of these factors was adipocytes, previously visualized as primarily fat warehouses. Adipocytes are now considered major endocrine tissues, secreting products derived from 30% of their expressed genes, including the hormone leptin and several "adipokines" that contribute to the new "endocrinology of obesity".[4-11,19-22] Leptin reports energy status, or "adiposity" to the hypothalamus, which then controls metabolism, appetite, and activity.

The hypothalamus mechanisms that control metabolism and appetite are incredibly complex and are beyond the scope of this article. However, some mention of the unique neurotransmitters is helpful. For example neuropeptide Y (NPY) and melanocortins have potent effects on appetite.[4,5] NPY stimulates appetite and appears to be inhibited by leptin. Melanocortins (MCH) inhibit appetite and are stimulated by leptin.[4,5] Animal models with defective MCH-4 receptors lack appetite control and become obese.

So, Why Do We Overeat?

Why do so many people overeat when they know it is unhealthy? Any comprehensive model of overeating should consider several levels of influence. One level of appetite control involves a complex balance between the hormonal and metabolic signals. This level is the focus of most cellular and molecular research (and most of this article). Level two is a sub-conscious neuronal "pleasure-reward system", based (simplistically) on the neurotransmitter dopamine, which influences and overlaps with these hormonal interactions. This system

originally rewarded behaviors that led to physical safety and wellbeing, such as successfully avoiding a saber-toothed tiger, building a warm fire, or gathering tasty berries. Unfortunately many negative activities such as drug or alcohol abuse and overeating can subvert the dopamine reward system.[14,19] In effect, negative behaviors are rewarded with the same dopamine elevations (by snorting cocaine, or consuming baskets of chips and salsa) that would ideally be reserved for behaviors that did more to secure safety and wellbeing.[14] Another level of decision-making includes subconscious habits, such as "compulsively cleaning up one's plate", even though full, or anticipating a feast every time you return home for the holidays. Finally our conscious choices may override all other levels. Sometimes we simply choose to eat for enjoyment or companionship, without regard for subconscious or molecular input. Whatever the motivation, consistent overindulgence in pleasurable foods quickly results in leptin resistance and diminished appetite control. Once hormonal restrictions are removed, the neuronal systems may continually reward overeating behaviors.

Leptin and the "Obesity Gene"

In 1973, Coleman demonstrated that mice with the ob/ob genotype become obese, with 5-fold more body fat than normal mice on identical diets.[4,5,7–10,20–22] In 1994, Jeffrey Friedman described leptin, a 16 kd peptide hormone product of the "obesity gene" (ob), which is secreted from fat cells.[4,5,20–22] Animals with the ob/ob genotype were leptin deficient. Without leptin, ob/ob mice had uncontrolled appetites (hyperphagia) and lacked thermogenesis (caloric expenditure to generate heat and without accumulation of ATP), causing development of obesity, insulin resistance, and diabetes.[4,11,20] The incredible hyperphagia that leads leptin-deficient mice to eat until their size prevents them from reaching their food, also causes leptin resistant mice (fa/fa genotype) to do the same.[4, 11, 20–23] Insulin resistance and diabetes in leptin-deficient mice were reversed by infusion of leptin or adenovirus-mediated insertion of the leptin gene.[20–23] Leptin levels increase with adipocyte mass, and elevated leptin levels provide feedback to the hypothalamus concerning energy reserves.[4,5,20-22] The leptin gene, therefore was widely hailed as the "obesity gene" and millions hoped. for an easy and quick solution to their weight problems[4,5] However, obese patients are rarely leptin deficient, more often exhibiting elevated leptin levels and leptin resistance.[4,5,11,15,16] This does not diminish leptin's impact on the subject of obesity. As with diabetes, the hormone resistant condition can be as problematic as the deficiency state.

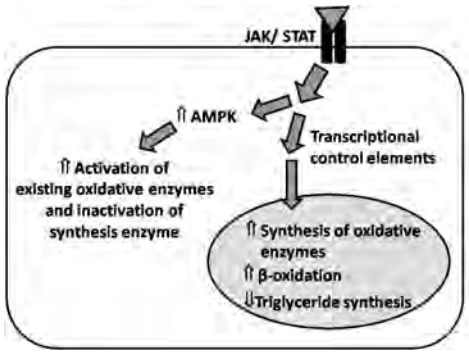
Leptin's Mode of Action

Leptin binds to cell surface receptors, activating a signaling system commonly used by cytokines (designated JAK-STAT).[9,10,19–21] As shown in Figure 3A, the system branches to activate the AMP-activated protein kinase (AMPK) system and various transcriptional control elements (designated PPARs, SREBPs, among others). Thus, leptin signaling includes immediate activation/deactivation of existing enzymes and transcriptional control of the amount of enzyme present.[10,12,21,25–3] The AMPK system is often described as the cell's "energy gauge" because it responds to the relative amounts of AMP and ATP.[12] Note that leptin's activation of the AMPK signaling sequence is AMP-independent and overrides the intracellular gauge in favor of the external energy status. In liver and muscle cells, leptin binding leads to an activation of the AMPK system, while leptin binding to hypothalamic receptors decreases AMPK activity and tells the hypothalamus when to suppress appetite and increase caloric expenditure.[30]

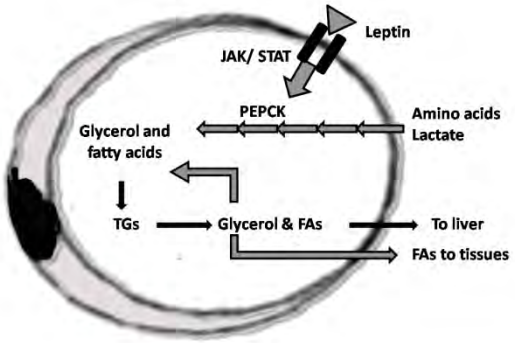
Leptin Limits Abdominal Fat Deposition

Roger Unger and others suggest that leptin's primary role is not prevention of obesity, but protection of non-adipose tissues from excessive lipid deposition.[9,10] Leptin initially limits abdominal fat deposition (ectopic fat or visceral adipose tissue, VAT, see Figures 3 and 4). Notice that both AMPK activation and the transcriptional signals discussed above promote increased fatty acid oxidation and block TG synthesis in liver and muscle.[9,10,21] Leptin sends a different message to adipocytes, where lipid synthesis and storage are promoted.[9,10] Thus, by promoting β-oxidation in non-adipose tissues and the TG synthesis in fat cells, leptin

directs fat deposition toward adipocytes and limits ectopic fat deposition.[9,10]

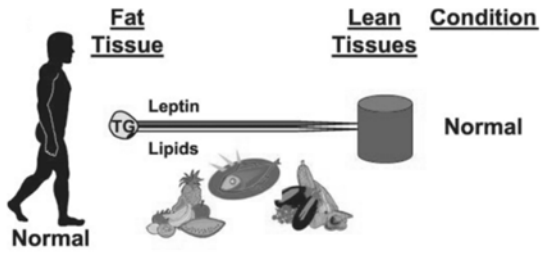


A. Leptin binding to cell surface receptors (JAK/STAT signaling system) causes tissue specific responses at both the level of gene transcription and phosphorylation of existing enzymes. In non-adipose tissues, these actions result in increased β-oxidation and decreased triglyceride (TG) synthesis. Thus, non-adipose tissues are protected from producing too many TGs (ectopic fat). In the hypothalamus, adenosine monophosphate-activated protein kinase (AMPK) is decreased, leading to appetite suppression, thermogenesis, and increased physical activity.

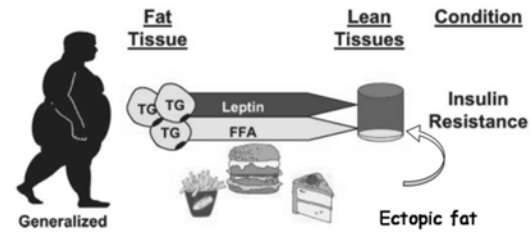


B. Lipid buffering in adipocytes involves a "futile cycle" of lipolysis, followed by re-esterification of fatty acids (FAs) and glycerol to reform TGs. The glycerol liberated by lipolysis is not reused, but is exported to the liver for gluconeogenesis. Thus, glycerol must be replaced through the process of glyceroneogenesis. This multi-step process is controlled by the enzyme phosphoenolpyruvate carboxykinase (PEPCK). Approximately 40% of FAs released by lipolysis are re-esterified by this lipid buffering system. Lipid buffering prevents large amounts of free fatty acids (FFAs) from entering plasma. For additional explanation, see reference 16.

Figure 3: Leptin's Signaling and the Lipid Buffering Cycle



A. Normal individual is on a good diet and healthy lifestyle. Occasional excess calories cause increased leptin and thermogenic metabolism to burn excess calories. Lean tissues have minimal ectopic fat.



B. Chronic overindulgence causes leptin resistance and massive ectopic fat deposition occurs in and around visceral organs.

Figure 4: Development of Obesity and Deposition of Ectopic Fat Modified with permission from Unger RH, Biochimie 2005; 87: 57–64.

Normal rats on 60% fat diets became obese, and deposited 3-fold more fat in their liver. Leptin-deficient animals had ravenous appetites, developed insulin resistance, and deposited up to 100-fold more hepatic triglycerides (TGs), even on 6% fat diets.[9,10,20] Leptin replacement controlled appetites, reversed insulin resistance, and decreased liver TGs.[9,10,20,24] in deficient animals. Similarly, leptin-deficient rats fed high sucrose diets, deposited abdominal fat, with increased liver export of TGs.[9,10,20] Again, leptin infusion caused rapid decreases of TGs in both liver and plasma.[24]

Leptin normally limits abdominal fat and promotes expansion of subcutaneous fat tissues.[27,31,32] Leptin resistance lowers metabolic rates, increases appetite, and leads to limited physical activity, ultimately causing abdominal obesity and expansion of metabolically hyperactive and toxic VAT (Figure 3).[4-11]

Lipid Buffering and Re-esterification

Elevated levels of free fatty acids (FFAs) play a key role in the development of obesity and the associated lipotoxicity.[9,10,20] Lipolytic release of FFAs and glycerol is catalyzed by hormone sensitive lipase (HSL) during fasting conditions (low insulin: glucagon ratio).[12] Approximately 40% of FFAs released by lipolysis are resynthesized to TGs without leaving the fat cell. This futile cycle "buffers" the body from large fluctuations of serum FFA.[9,10,12,31,32] Glyceroneogenesis, controlled by phosphoenolpyruvate carboxykinase, or PEPCK, produces glycerol to complete this cycle, because the glycerol released by lipolysis is exported, rather than recycled.[32-34] As seen in Figure 3B, animals that overexpress PEPCK were able to effectively buffer serum lipids when on a normal diet, minimizing ectopic fat, maintaining insulin sensitivity, and having lower serum FFAs and TGs.[32-34] However, on a high fat diet, these animals were ineffective at lipid buffering; they became obese, displayed insulin and leptin resistances, and had elevated FFAs and TGs.[33]

Unger suggests that throughout evolution leptin elevations provided a survival advantage by curbing appetite, increasing metabolism, and restricting lipid deposition after feasting.[9,10,20] He asserts that leptin prevents excessive weight gain when food is plentiful, promoting a trimmer physique for future food-gathering. Hypercaloric diets override this mechanism, resulting in leptin resistance, ectopic fat deposition, and lipotoxicity.[4,5,9,10,20]

Where Do Adipocytes Originate?

Pre-adipocytes, which originate from the macrophage cell line, are phagocytic, express macrophage-specific cell surface antigens, and secrete high levels of pro-inflammatory adipokines, such as TNF-α and IL-6.[34, 35] These macrophage-like characteristics are absent or muted in mature adipocytes. Occasional overeating causes expansion of storage within pre-existing subcutaneous adipocytes and stimulates thermogenesis to eliminate excess calories. Chronic overindulgence results in leptin resistance and facilitates recruitment and maturation of pre-adipocytes into the larger adipocytes of VAT.[32-35]

Leptin Resistance Leads to "Starvation Physiology"

Fasting conditions decrease caloric requirements as metabolism "downshifts" in response to high insulin/glucagon ratios. Leptin deficiency (in ob/ob mice) or resistance (in fa/fa mice) induces "starvation physiology" that includes a dramatic shift beyond catabolic metabolism and reduced BMR, to include hyperphagia, and decreases in physical activity, body temperature, immune function, and fertility.[9,10,20-22] Leptin-deficient or resistant mice exhibit these physiologic and behavioral changes that promote weight gain and obesity, even when caloric intake is matched with those of normal-weight control mice.[9,10,22] These changes are eliminated by leptin infusion or insertion of functional genes.[9,10,20,24]

Many Roads Converge onto the Obesity Highway

As illustrated in Figure 2, there are many "entrance ramps" onto the obesity highway. Each ramp contributes to a PEB, resulting from some combination of increased consumption and decreased caloric expenditure. Before merging onto the obesity highway, hormonal feedback systems effectively compensate for wide daily variations in food intake and exercise. However, consistent caloric excesses inevitably lead to leptin resistance and obesity. Figure 2 shows that leptin resistance often precedes insulin resistance and impaired glucose metabolism.[4,5,9,10] Increasing hormonal resistance accelerates progression on the obesity highway, as the natural deterrents (leptin) to weight gain are removed, making it more difficult to exit the highway.

The following section describes a number of "entrance ramps" onto the obesity highway. A subsequent article describes several cases that include the metabolic and endocrine profiles of obese patients.

Cortisol, Coping, and Comfort Food

Chronic stress is manifest in many aspects of modern society, initiating the chronic stress-response network, including elevation of cortisol as shown in Figure 5.[6,13]

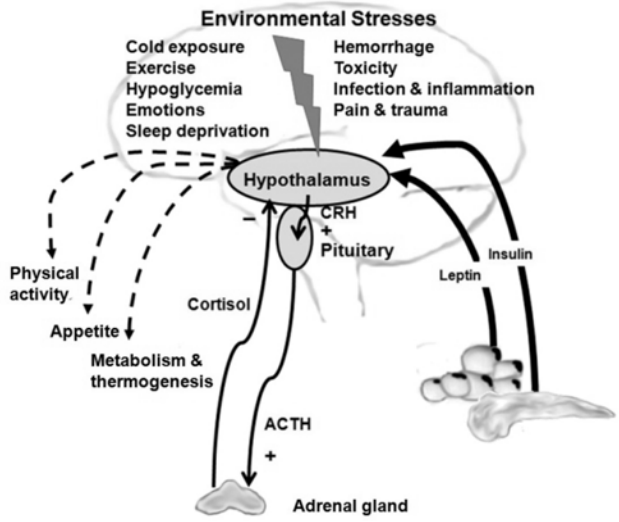


Figure 5: Stimulation & Hormonal Feedback to Hypothalamus
Many outside stimuli are integrated by the hypothalamus with hormonal and metabolite feedback systems that provide status reports concerning internal conditions. For example, glucose and fatty acids would indicate current energy status, while insulin and leptin report on energy storage or "adipodisity."

The hypothalamus helps control appetite, metabolism, thermogenesis, and physical activity. It also releases corticotropin-releasing hormone (CRH), which signals the pituitary to release adenrocorticotropic hormone (ACTH). Finally, ACTH stimulates the release of cortisol.

Failure of these feedback systems (hormonal resistance) is a critical landmark on the obesity highway, because it perpetuates the positive energy balance by allowing increased appetite, decreased physical activity, starvation metabolism, and deposition of abdominal fat.

Studies of animal models demonstrate stress-induced hyperphagia and a preference for "comfort" foods that are high in fats and carbohydrates.[6,13] In humans, high cortisol levels seem to promote compulsive or pleasurable, stress-relieving activities, such as eating sweet or fatty foods, taking drugs, and drinking alcohol.[13] Cortisol promotes overeating and redistribution of energy reserves (toward abdominal fat) by increasing gluconeogenesis and TG synthesis, fueled by increased catabolism of muscle protein.[6,12,13] Relieving stress by "vegging out" with a TV remote and plate of comfort food is a popular "entrance ramp" onto the highway to obesity.

Cushing disease

Cushing disease is hypercortisolemia that originates from endocrine dysfunction rather than stress. Classic symptoms of Cushing disease are the round "moon face" and "buffalo hump" accompanied by the characteristic central obesity with thin appendages. Cushing disease causes substantial muscle wasting, thinning of skin, immune suppression, and increased bruisability and bleeding, all associated with protein degradation to support gluconeogenesis.[6,11-13]

Pleasure-Seeking Lifestyle Choices and Habits

Obesity often results from pleasure-seeking choices, reinforced by the dopamine pleasure/reward system.[14] Many unfortunate choices result from habits learned in childhood (and unchanged in adulthood), behaviors influenced by slick advertising, lack of physical activity or exercise, and consumption of readily available, high calorie foods. Current cultural emphasis on "immediate gratification" also favors pleasurable eating over exercise or dietary restriction.

Genetic Predisposition

A strong genetic influence on the development of obesity is suggested by close similarities in BMIs found in identical twins raised apart.[15,16] Analysis from family and twin studies estimates that 30–70% of body mass variation within the population results from inherited factors.[15,16] However, experts agree that inheritance of a tendency toward obesity is usually not due to a single gene defect but is, instead, polygenic. Studies show that each individual gene typically exerts a modest impact on BMI.[4,5,7,15,16] Very rare exceptions are monogenic defects, such as deficiencies of leptin, leptin receptor, or genes controlling hypothalamic feedback. In all of these cases, the result is loss of appetite suppression and early-onset obesity.[4,5,15,16] Less dramatic polymorphisms within human genes for leptin, leptin receptors, adiponectin (ADN) and ADN receptors exist, but most variants are associated with minor changes in weight or BMI.[15,16]

Several large population studies, using genomic and bioinformatics techniques have found specific alleles of a gene (designated FTO) that is associated with 1–3 kg

weight increases.[36] Obviously, this small weight gain seldom raises a normal BMI into the obese range.

Hypothyroidism Reduces BMR

Thyroid hormones control our basal metabolic rate (BMR), and hypothyroidism, most commonly an autoimmune disease called Hashimoto disease, reduces the BMR by 10-15%. Such consistent reductions in BMR make weight gain difficult to avoid. Patients with Hashimoto disease also tend to suffer from exercise and cold intolerance, lethargy, and constipation.[12,37] Fortunately, thyroid hormone supplementation can moderate the effects of Hashimoto disease.[11,12,37]

Alcohol, Drugs, and Neurochemistry

Many addictive or compulsive behaviors, including alcoholism, are often associated with dopamine. Obese patients often express fewer dopamine receptors, similar to levels found in people addicted to drugs and/or alcohol.[14] Dopamine is a component of the brain's "pleasure center", and drugs such as cocaine potentiate dopamine activity by blocking its re-uptake. This provides a neurochemical link between obesity and obsessive-compulsive behaviors, which are 25% more likely to occur in obese patients compared to patients of normal weight.[14] Additionally, the β-adrenergic and sympathetic nervous systems are involved with thermogenic response.[39,40] Mice with β-adrenergic receptor deficiencies lacked the thermogenic response to over-nutrition and became obese, compared to control mice of normal weight.[40]

Some prescription drugs, such the second-generation antipsychotics (e.g. olanzapine and clozapine) are associated with significant weight gain, abdominal fat deposition, and insulin resistance.[14, 38] Interestingly, these drugs appear to affect the AMPK phosphorylation system, decreasing hypothalamic control of appetite.[38]

Lifestyles Devoid of Physical Activity

Many jobs and many leisure activities require little or no physical activity and make a PEB difficult to avoid. Typical Americans consume roughly 100 calories/day more than in 1900, but burn several hundred fewer calories/day during physical activity.[2] For example, an employee at a computer-dominated job might burn 500 work-related calories per day, compared to construction or farm workers, who burn more than 1500 work-related calories.[12] Unfortunately, inconsistent vigorous workouts at the gym seldom burn enough calories to cause substantial weight loss without dietary constraints. Since progression along the obesity highway is fueled by a PEB, a long-term commitment to a combination of exercise and diet provides the best "exit ramp".[4,5,41,42]

Yo-Yo Diets: Fighting Vainly Against Our Hypothalamus

Dieters know the feeling of "swimming against the current" to lose weight, and the term "yo-yo diet" describes our body's resistance to weight loss. Popular myth suggests that body weight skyrockets whenever we look away, but endocrinology indicates that our hypothalamus initially limits weight gain above our current weight or "set point". See Table 1 for a summary of the effects of energy balance on hormones and metabolism.

Dieting decreases caloric intake and, at weights below the set point, decreased leptin levels signal the hypothalamus of diminished "adiposity" (energy storage). Fasting metabolism results in decreased caloric requirements, increased appetite, and limited physical activity.[12, 39, 40, 41, 42] Another peptide hormone from the GI tract, called ghrelin (or the "hunger hormone") also promotes increased appetite during dieting [43].

Above the set point, elevated leptin signals the hypothalamus that energy reserves are adequate. This results in appetite suppression, increased anabolic metabolism and thermogenesis, and encourages physical activity. However, chronic "over-nutrition" causes leptin/insulin resistances, negating hormonal feedback with its associated appetite and metabolic effects.[12, 41,42]

Obesity's Effect on Lifespan

Given the depressing list of co-morbidities associated with obesity (described in the accompanying article), it is not surprising that weight loss has a positive impact on longevity. Numerous studies have documented the metabolic and health benefits of weight loss, by either

Table 1: Interaction of Hormones and Metabolism Resulting From Dietary Changes

Status of Energy Stores, Weight Change	Hormonal Signals	Metabolic Rate Storage or Starvation	Appetite or Satiety	Physical Activity	Net Weight Gain or Loss
Negative energy balance (diet); weight loss	⇓ Leptin ⇓ Insulin	Starvation metabolism ⇓ BMR	⇑ Appetite	⇓ Physical activity conserve energy	Promotes weight gain
Neutral energy balance; No weight change	⇔ Leptin ⇔ Insulin	Normal metabolism	Normal appetite	Normal physical activity	Promotes current weight
Positive energy balance; (occasional feasting) little weight gain	⇑ Leptin ⇑ Insulin	Storage metabolism ⇑ BMR	⇓ Appetite	⇑ Physical activity	Promotes current weight or minimizes weight gain
Chronic positive energy balance; obesity	⇑ Leptin (resist) ⇑ Insulin (resist)	Starvation metabolism ⇓ BMR	⇑ Appetite	⇓ Physical activity conserve energy	Promotes weight gain

diet or exercise.[4,5,7-10,41,42] Experts now predict a general decrease in lifespan for the first time in centuries, as obesity and metabolic syndrome overwhelm medical advances.[46] As described in the accompanying article, surplus lipids lead to lipotoxicity and apoptosis, while adipokines promote inflammation, atherosclerosis, and CVD.[17]

Unfortunately, given the complexities in development of obesity and the cellular damage caused by lipotoxicity and atherosclerosis, dietary "magic bullets" seem unlikely. While the new "endocrinology of obesity" offers hope for new prevention strategies, it also reaffirms the benefits of diet and exercise in controlling stress and reversing obesity and hormone resistance.[4,5,41-43] Caloric restriction, even to levels slightly below accepted "requirements", tends to extend lifespan.

Benefits of Diet and Exercise

Since obesity results from chronic over-nutrition, successful weight loss requires a "healthy" negative energy balance. Although exercise options are often limited for obese patients, finding appropriate ones is an important lifestyle change, with benefits beyond simply burning calories. When combined with diet, an exercise regimen helps counteract the usual "metabolic downshift" and decreased physical activity directed by the hypothalamus. Exercise promotes anabolic metabolism, increases BMR, reduces stress, and promotes hormonal sensitivity by up-regulating receptors and signaling pathways.[4,32,34] Additionally, exercise can provide an alternate method of stimulating the brain's pleasure center, which may have previously been dominated by unhealthy eating behaviors. A healthy diet and exercise can help decelerate progress along the obesity highway and even provide an exit ramp.

Approaches to Drug Treatments

Drugs such as sibutramine and rimonabant are appetite suppressants that modify our perceptions of hunger in the brain.[4,35,36] Orlistat (sold as Alli) is an FDA-cleared drug that blocks intestinal fat absorption.[4,35] Our knowledge of signaling pathways for control of appetite and metabolism enables the design of specific inhibitors or agonists. For example, neuropeptide Y (NPY) is a potent stimulator of appetite. Leptin inhibition of NPY

explains part of its role in appetite suppression. Melanocortins also cause neuronal inhibition of appetite. Animal models with defective melanocortin-4 receptors become obese.[4,5,47-49] Other appetite-signaling pathways include obvious targets, such as ghrelin, the "hunger hormone".[4,47-49]

The thiazolidinediones (TZDs) are specific activators of peroxisome proliferator–activated receptor (PPAR) and have been shown to improve insulin sensitivity in type 2 diabetic patients.[11] TZDs have a direct antidiabetic effect on glucose metabolism in skeletal muscle and liver.[12] In addition, TZDs increase insulin sensitivity by increasing lipid storage capacity of adipose tissue and reducing circulating FFA and triglyceride levels.[13] TZDs decrease FA release from adipose tissue by increasing FFA re-esterification via the induction of both phosphoenolpyruvate carboxykinase (PEPCK), a regulatory enzyme of glyceroneogenesis, and glycerol kinase.[14,15]

Other approaches include inhibition of adipocyte enzymes or transporters to prevent uptake or synthesis of TGs. Finally, stimulation of "fat burning" mechanisms, by "uncoupler proteins," may enable burn-off of unwanted calories. Although many dietary supplements and over-the-counter formulations already claim success, availability of drugs that have cleared clinical trials and obtained FDA approval is several years away.[4,5,47-49]

Conclusion

Leptin normally provides energy status reports to the hypothalamus, which then controls appetite and energy expenditure. Obesity generally involves a PEB that exceeds the adipocyte's capacity to store fat and results in resistance to leptin. Once leptin resistance occurs, appetite suppression and control of energy expenditure are lost and starvation physiology defaults to conditions that actually promote continued weight gain (see Figure 6). The alarming list of physiologic changes includes: decreased metabolism, hyperphagia, chronic inflamemation, deposition of abdominal fat, dysregulation of carbohydrate and lipid metabolism (and elevated glucose and FFAs), lipotoxicity, development of atherosclerosis, and CVD. All of these outcomes result in acceleration along the obesity highway toward metabolic syndrome.

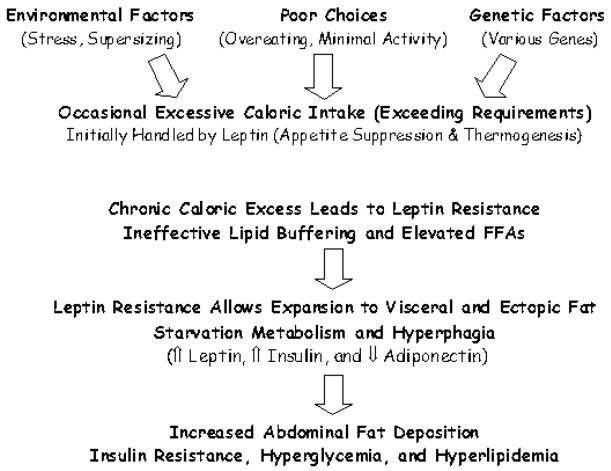


Figure 6: Progression Along the Obesity Highway

Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this Focus section. Email responses to westminsterpublishers @comcast.net. In the subject line, please type "CLIN LAB SCI 23(1) FO OBESITY AND METABOLIC SYNDROME". Selected responses will appear in the Dialogue and Discussion section in a future issue. Responses may be edited for length and clarity. We look forward to hearing from you.

REFERENCES

1. Ogden CL, Carroll MD, McDowell MA, and others. Obesity among adults in the United States— no change since 2003–2004. NCHS data brief no 1. Hyattsville, MD: National Center for Health Statistics. 2007.
2. http://www.cdc.gov/nccdphp/dnpa/Obesity referenced 11/10/08.
3. Popkin B. The world is fat. Sci Amer 2007; 297:88–95.
4. Flier JS, Flier EM. What fuels fat? Sci Amer 2007; 297: 72–81.
5. Friedman JM. Obesity in the new millennium. Nature 2000; 404; 632–34.
6. Dallman MF, La Fleur S, Pecoraro NC, and others. Minireview: glucocorticoids—food intake, abdominal obesity, and wealthy nations in 2004. Endocrinology 2004; 145:2633–8.
7. Wilding J. Obesity. Medicine 2006; 34: 501–5.
8. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000;106:473–81.
9. Unger RH. Hyperleptinemia: protecting the heart from lipid overload. Hypertension 2005; 45:1031–4.

10. Unger RH, Zhou YT, Orci L. Regulation of fatty acid homeostasis in cells: Novel role of leptin. Proc Natl Acad Sci 1999; 96: 2327–32.
11. Burtis CA, Ashford ER, Bruns DE. Tietz Fundamentals of Clinical Chemistry, 6th Edition, 2008, Saunders-Elsevier, St. Louis, MO.
12. Lieberman M, Marks AD. Marks' Basic Medical Biochemistry, 3rd Edition, 2009, Lippincott, Williams, & Williams, Philadelphia. PA.
13. Dallman MF, Pecoraro N, Akana SF, and others. Chronic stress and obesity: a new view of ''comfort food'' Proc Natl Acad Sci 2003; 100: 11696–701.
14. Wang GJ, Volkow ND, Logan J. Brain dopamine and obesity. Lancet 2001; 357 (9253): 354–7.
15. O'Rahilly S, Farooqi IS. Genetics of obesity. Phil Trans R Soc B 2006; 361: 1095–105.
16. Lyon HN, Hirschhorn JN. Genetics of common forms of obesity: a brief overview. Am J Clin Nutr 2005; 82 (Suppl): 215S–17S.
17. Gade, W, Schmidt, J, Collins,M, and others. Beyond Obesity: The Diagnosis and Pathophysiology of Metabolic Syndrome. Clin. Lab. Sci. 2009; 23 (1); 51-62.
18. Buckingham L, Flaws ML. Molecular Diagnostics: Fundamentals, Methods, & Clinical Applications. F A Davis Company, Philadelphia, 2007.
19. Woods SJ, Seeley RJ, Porte D Jr, and others. Signals that regulate food intake and energy. Homeostasis Science 1998; 280: 1378–83.
20. Unger RH. Weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. Endocrinol 2003; 144: 5159–65.
21. Friedman J, Halaas J. Leptin and the regulation of body weight in mammals. Nature 1998; 395: 763–70.
22. Maeda K, Okubo K, Simomura I, and others. Analysis of expression profile of genes in the human adipose tissue. Gene 1997; 190: 227–35.
23. Pelleymounter M, and others. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995; 269: 540-43.
24. Truett GE, Bahary N, Friedman JM, and others. Rat obesity gene fatty (fa) maps to chromosome 5: Evidence for homology with the mouse gene diabetes (db) Proc Natl Acad Sci 1991; 88: 7806–9.
25. Shimomura I, Hammer R, Ikemoto S, and others. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. Nature 1999; 401 (6748): 73–6.
26. Unger RH. The physiology of cellular liporegulation. Ann Rev Physiol 2003; 65:333–47.
27. Brabant G, Muller G, Horn R, and others. Hepatic leptin signaling in obesity. FASEB J 2005; 19: 1048–50.
28. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocrin Rev 2000; 21: 697–738.
29. Unger RH, Orci L. Diseases of liporegulation: new perspective on obesity and related disorders. FASEB J. 2001; 15:312–21.
30. Andersson U, Filipsson K, Abbott CR, and others, AMP-activated protein kinase plays a role in the control of food intake. J Biol Chem 2004; 279: 12005–8.
31. Franckhauser S, Munoz S, Pujol A. Increased fatty acid re-esterification by PEPCK overexpression in adipose tissue leads to obesity without insulin resistance. Diabetes 2002; 51: 624–30.
32. Franckhauser S, Munoz S, Elias I, and others, Adipose overexpression of phosphoenolpyruvate carboxykinase leads to high susceptibility to diet-induced insulin resistance and obesity. Diabetes 2006; 55:273–80.
33. Sun Y, Liu S, Ferguson S, and others, Phosphoenolpyruvate carboxykinase overexpression selectively attenuates insulin signaling and hepatic insulin sensitivity in transgenic mice. J Biol Chem 2002; 277 23301–7.
34. Charrie`re G, Cousin B, Arnaud E, and others, Preadipocyte conversion to macrophage, evidence of plasticity. J Biol Chem 2003; 278; 9850–5.
35. Harkins JM, Moustaid-Moussa N, Chung Y. Expression of interleukin-6 is greater in preadipocytes than in adipocytes of 3T3-L1 cells and C57BL/6J and ob/ob mice. J Nutr 2004; 134: 2673–7.
36. Frayling TM, Timpson NJ, Michael N, Weedon MN, and others. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007; 316: 889–94.
37. Goglia F, Moreno M, Lanni A. Action of thyroid hormones at the cellular level: the mitochondrial target. FEBS Lett 1999; 452: 115–20.
38. Kim SF, Huang AS, Snowman AM, and others. Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. Proc Natl Acad Sci 2007; 104: 3456–9.
39. Lowell BB, Bachman ES, β-adrenergic receptors, diet-induced thermogenesis, and obesity. J Biol Chem 2003; 278, 29385–8.
40. Bachman ES, Dhillon H, and Zhang CY. β-AR signaling required for diet-induced thermogenesis and obesity resistance. Science 2002; 297: 843–45.
41. Achten J, Jeukendrup AE. Optimizing fat oxidation through exercise and diet. Nutrition 2004; 20: 716–27.
42. Ross R, Dagnone D, Jones PJH. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. Ann Intern Med 2000; 133: 92–103.
43. Mark AL. Dietary therapy for obesity: an emperor with no clothes. Hypertension 2008; 51: 1426–34.
44. Liebel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med 1995; 332:621–8.
45. Cummings DE, Weigle DS, Frayo RS, and others. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002; 346:1623–30.
46. Olshansky SJ, Passaro DJ. A potential decline in life expectancy in the United States in the 21st century. NEJM 2005; 352: 1138–45.

47. Rouhi AM. Metabolic syndrome. Chem Eng News 2004; 82:83–99.
48. Campfield LA, Smith FJ, Burn P. Strategies and potential molecular targets for obesity. Treatment Science 1998; 280: 1383–7.
49. Holness MJ, Leptin: a central role in an expanding answer to weight loss. Endocrinol. 2007; 148: 5601–3.