Childhood obesity: behavioral aberration or biochemical drive? Reinterpreting the First Law of Thermodynamics

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SUMMARY

Childhood obesity has become epidemic over the past 30 years. The First Law of Thermodynamics is routinely interpreted to imply that weight gain is secondary to increased caloric intake and/or decreased energy expenditure, two behaviors that have been documented during this interval; nonetheless, lifestyle interventions are notoriously ineffective at promoting weight loss. Obesity is characterized by hyperinsulinemia. Although hyperinsulinemia is usually thought to be secondary to obesity, it can instead be primary, due to autonomic dysfunction. Obesity is also a state of leptin resistance, in which defective leptin signal transduction promotes excess energy intake, to maintain normal energy expenditure. Insulin and leptin share a common central signaling pathway, and it seems that insulin functions as an endogenous leptin antagonist. Suppressing insulin ameliorates leptin resistance, with ensuing reduction of caloric intake, increased spontaneous activity, and improved quality of life. Hyperinsulinemia also interferes with dopamine clearance in the ventral tegmental area and nucleus accumbens, promoting increased food reward. Accordingly, the First Law of Thermodynamics can be reinterpreted, such that the behaviors of increased caloric intake and decreased energy expenditure are secondary to obligate weight gain. This weight gain is driven by the hyperinsulinemic state, through three mechanisms: energy partitioning into adipose tissue; interference with leptin signal transduction; and interference with extinction of the hedonic response to food.

KEYWORDS addiction, insulin, leptin resistance, obesity, starvation

REVIEW CRITERIA

I searched for original articles focusing on energy balance and obesity in MEDLINE and PubMed from 1994 to 2005. The search terms I used were "insulin", "insulin resistance", "leptin", and "leptin resistance". All papers identified were English-language full-text papers. I also searched the reference lists of identified articles for further papers.

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INTRODUCTION

We are in the midst of an unprecedented rise in prevalence and severity of obesity, especially in children.[1] Although common wisdom dictates that obesity is an interaction between genetics and environment, the gene pool has not changed in the last 30 years, but the environment has. Examination of the BMI distribution histogram[2] demonstrates that even those at the lower end of the BMI curve are gaining weight. Whatever is happening is happening to everyone, suggesting an environmental trigger. This observation is also reflected in the increased prevalence of obesity in developing countries.[3] This review will address the relationship between changes in the environment and the neuroendocrinology of human energy balance, particularly as it applies to the current childhood obesity epidemic.

THE FIRST LAW OF THERMODYNAMICS

Energy balance obeys the First Law of Thermodynamics, which states: "The energy within a closed system remains constant". This law is usually interpreted as "If you eat it (energy intake), you must burn it (energy expenditure), or you will store it (weight gain)". This view is buttressed by studies of increased caloric intake[4] and decreased energy expenditure[5] in children. This interpretation of the First Law of Thermodynamics promulgates the idea that obesity is the result of pathologic behavior on the part of the obese person, which invokes the concept of personal responsibility, and permits absolution of responsibility by governments and the business community. The concept of personal responsibility is, however, not tenable in children. No child chooses to be obese. Obese children are ostracized by their peers, and their quality of life, as measured by self-reported distress, is comparable to those receiving cancer chemotherapy.[6] Young children, among whom obesity is rampant,[1] are not responsible for their food choices and are incapable of accepting personal responsibility.

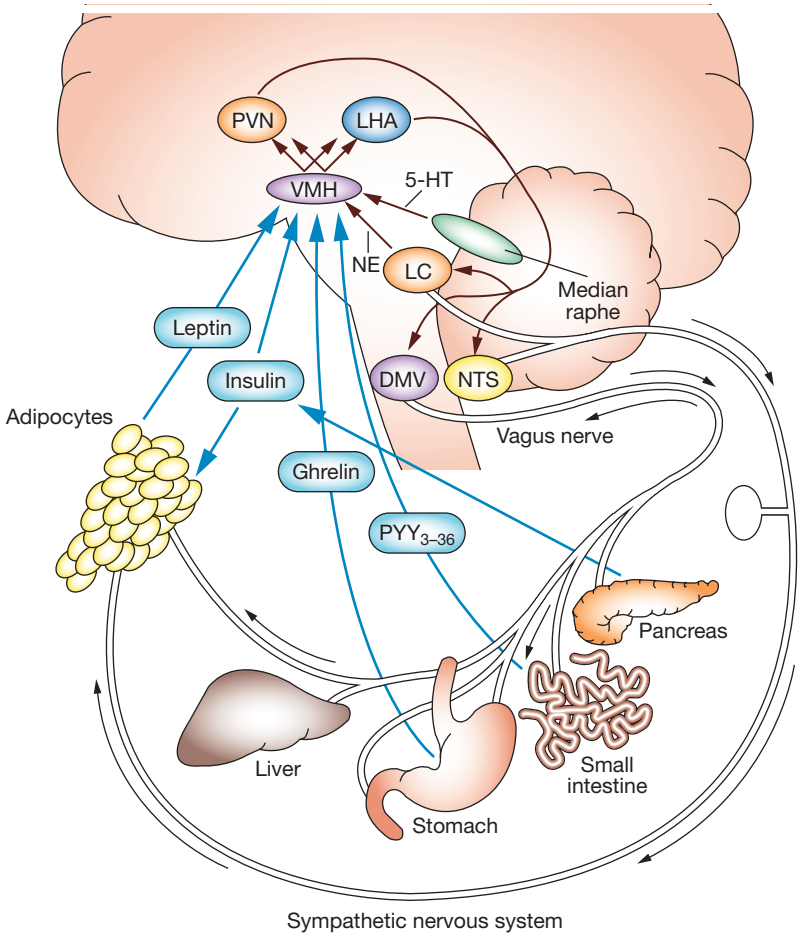

Figure 1 The homeostatic pathway of energy balance. Afferent (blue), central (brown), and efferent (white) pathways are delineated. The hormones insulin, leptin, ghrelin, and peptide $YY_{3–36}$ provide afferent information to the ventromedial hypothalamus, relating to short-term energy metabolism and energy sufficiency. From there, the ventromedial hypothalamus elicits anorexigenic (α-melanocyte stimulating hormone, cocaine-amphetamine regulated transcript) and orexigenic (neuropeptide Y, agouti-related protein) signals to the melanocortin 4 receptor in the paraventricular nucleus and lateral hypothalamic area. These signals lead to efferent output via the locus coeruleus and the nucleus tractus solitarius, which activates the sympathetic nervous system and causes adipocytes to undergo lipolysis, or via the dorsal motor nucleus of the vagus, which activates the vagus nerve and causes energy storage, both by increasing pancreatic insulin secretion, and (in rodents) by increasing adipose-tissue sensitivity to insulin.[9] Reproduced with permission from reference 9 © (2001) Elsevier Inc. Abbreviations: 5-HT, serotonin (5-hydroxytryptamine); DMV, dorsal motor nucleus of the vagus; LC, locus coeruleus; LHA, lateral hypothalamic area; NE, norepinephrine; NTS, nucleus tractus solitarius; PVN, paraventricular nucleus; $PYY_{3–36}$, peptide $YY_{3–36}$; VMH, ventromedial hypothalamus.

BEHAVIOR IS REALLY BIOCHEMISTRY

If obesity is a result of behavior, then behavior and/or lifestyle modification (BLM) should be effective in mitigating the process. Indeed, as a result of some individual successes,[7] BLM has become the cornerstone of therapy; however, BLM is not successful in the majority of obese children.[8] Behavior is defined as "a stereotyped motor response to a physiological stimulus". This definition implies that there are physiological bases underpinning behavior. This relationship is evident in many medical disorders, such as diabetes insipidus, narcolepsy, and schizophrenia. So, what is the physiology behind gluttony and sloth? And how does our current environment bring about these conditions?

THE HOMEOSTATIC PATHWAY OF ENERGY BALANCE

The hypothalamus orchestrates the neuroendocrine control of energy balance, via a complex homeostatic pathway that comprises three arms[9] (Figure 1). The first arm consists of afferent signals to the central nervous system (CNS). The ventromedial hypothalamus (VMH), consisting of the arcuate and ventromedial nuclei, contains first-order neurons with hormone receptors that receive peripheral signals related to adiposity (leptin), metabolism (insulin), hunger (ghrelin), and satiety (peptide $YY_{3–36}$). The second arm consists of second-order neurons, which transduce these hormonal signals to the paraventricular nucleus (PVN) and lateral hypothalamic area. These signals are either anorexigenic (e.g. α-melanocyte stimulating hormone, cocaine-amphetamine-regulated transcript) or orexigenic (e.g. neuropeptide Y, agouti-related protein). The PVN and lateral hypothalamic area integrate these signals via melanocortin 4 receptor (MC4-R) occupancy to alter caloric intake and energy expenditure.[10] The third arm consists of efferent signals via the autonomic nervous system. The sympathetic nervous system (SNS) promotes energy expenditure, whereas the vagus nerve promotes energy storage[11] (see below). Insulin is part of both the afferent and efferent pathways. Unraveling its dual role provides valuable insights into the pathogenesis of obesity.[12]

The afferent pathway

Leptin as an afferent signal

The adipocyte hormone leptin conveys a signal of peripheral energy sufficiency to neurons in the arcuate nucleus expressing the leptin receptor.[13] Leptin increases α-melanocyte stimulating hormone and inhibits neuropeptide Y, which reduces food intake and increases SNS activity.[14] Leptin is a permissive, afferent signal for the initiation of high-energy processes, such as puberty and pregnancy.[13]

Insulin as an afferent signal, and its similarity to leptin

Insulin receptors co-localize to the same subpopulation of arcuate neurons as do leptin receptors.[15] Insulin gains access to the CNS via a saturable transporter.[16] In animals, acute intracerebroventricular insulin infusion decreases feeding behavior, induces satiety, and activates the SNS, similarly to leptin.[17] Insulin and leptin both acutely activate the insulin receptor substrate 2–phosphatidylinositol 3 kinase (IRS-2–PI3K) second-messenger system in VMH neurons,[18] which increases neurotransmission of the central anorexigenic signaling pathway. The importance of insulin action in the CNS was demonstrated by production of mice in which the insulin receptor was knocked out specifically in the brain; these mice cannot transduce CNS insulin signals,[19] and they become hyperphagic, obese, and infertile—similar to leptin-deficient (*ob/ob*) and leptin-resistant (*db/db*) mice. Similarly, knockout of IRS-2 within the CNS interferes with the afferent signal and produces obesity.[20,21] These data suggest that insulin mediates an acute afferent signal similar to that mediated by leptin.[22]

The efferent pathway

The sympathetic nervous system and energy expenditure

Anorexigenic pressure by leptin, which alters MC4-R occupancy in the PVN,[10] leads to decreased food intake, whereas MC4-R activation in other CNS sites promotes increased energy expenditure, through activation of the SNS[23] (Figure 2A). For instance, leptin administration to *ob/ob* mice promotes increased lipolysis in brown adipose tissue, increased thermogenesis, and increased movement, all associated with increased energy expenditure and weight loss;[24] however, this effect is not seen in the Zucker rat strain, which has a mutation in the leptin receptor.[25]

SNS activation increases energy expenditure through glycogenolysis, and through glucose and fatty acid oxidation via β_2-adrenergic receptor activation in skeletal muscle.[26] SNS activation also promotes lipolysis in adipocytes, through activation of the β_3-adrenergic receptor, (which increases expression and activity of uncoupling proteins UCP 1 and UCP 2[23]) and via hormone-sensitive lipase, which is responsible for breakdown of triglyceride to free fatty acids (Figure 2B). Lastly, the SNS activates the α_2-adrenergic receptor on β cells and reduces insulin release (Figure 2C).

The vagus nerve and energy storage

Vagus nerve activation opposes SNS activation, and promotes energy storage. The vagus nerve slows the heart rate to reduce myocardial oxygen consumption, and it promotes peristalsis and energy substrate absorption from the alimentary tract. In rats, vagal efferent fibers have synapses on adipocytes (Figure 2B) and vagal activation improves insulin sensitivity and increase the clearance of energy substrate into adipose tissue (not yet demonstrated in humans).[27] Vagal modulation of β-cell function promotes insulin hypersecretion and increases substrate partitioning into adipose tissue (Figure 2C).[28] This action is exemplified by the M3 muscarinic receptor knockout mouse strain, which remains lean with low insulin secretion.[29]

The leptin 'set-point' and the starvation response

Examination of weight-loss patterns in response to BLM, and the effects of the obesity drugs dexfenfluramine, sibutramine, and orlistat demonstrate remarkable similarities.[30] Each exhibits a weight-loss phase of 4 months, followed by a plateau. Although reduced dietary intake and/or absorption continues, the plateau is inviolate. Although originally viewed as a result of noncompliance or drug tachyphylaxis, this plateau is actually due to a decline in resting energy expenditure (REE) that occurs in response to the decline in serum leptin, which offsets the reduced caloric intake. This reduction in REE is termed the "starvation response". Leibel *et al.*[31] showed that REE is dependent on nutritional status; in the energy-replete state, REE is 50 kcal/kg fat-free mass, whereas when weight is reduced, REE is reduced to 40–42 kcal/kg fat-free mass.[32] Thus, starvation results in a 20% increased efficiency of energy use.[33] Reductions in REE (e.g. that result from starvation or hypothyroidism) are associated with fatigue, malaise, decreased physical activity, and decreased quality of life. Conversely, factors that increase REE—primarily stimulants (e.g. caffeine, a phosphodiesterase inhibitor that stimulates fat oxidation)—increase wellbeing and physical activity.[34,35]

It has been postulated that each human has an individual leptin 'set-point'—a leptin concentration at which the hypothalamus perceives a state of energy sufficiency[13]—that is probably genetically determined. Leptin concentrations drop precipitously during periods of short-term

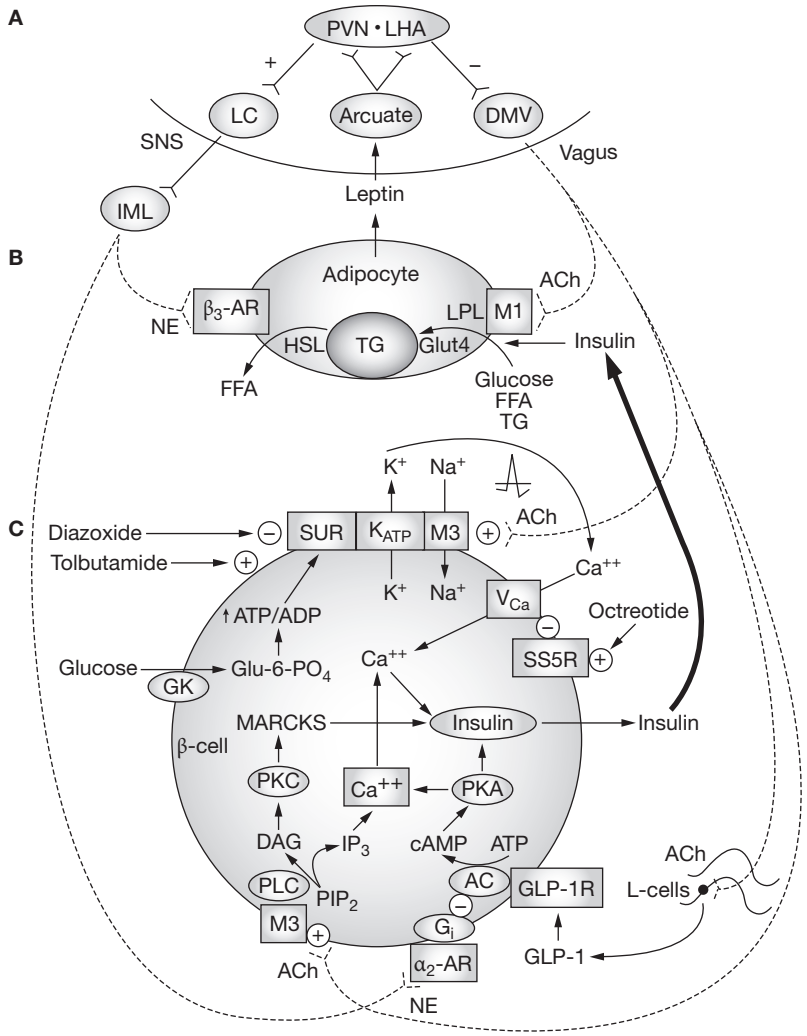

Figure 2 Legend opposite.

fasting (within 12 h), and decline faster than body fat stores are depleted.[36] This drop in leptin is interpreted by the hypothalamus as diminished energy reserve, which invokes the starvation response (Figure 2) and brings about alteration of efferent autonomic output in order to conserve energy.[37] Reduction in adrenergic tone reduces skeletal muscle energy usage and physical activity. Increased vagal tone reduces myocardial oxygen consumption, increases gastric motility (which increases appetite and alimentary absorption), increases adipose tissue insulin sensitivity, and increases pancreatic insulin secretion. These adaptations partition more energy to adipose tissue and raise leptin levels back to the energy-replete state.[11]

The concepts of the leptin set-point and the starvation response are exemplified by the leptin-deficient state. Both *ob/ob* mice and leptin-deficient humans exhibit a chronic starvation response, characterized by decreased SNS tone leading to decreased REE, decreased physical activity, and decreased reproductive capacity; along with increased vagal tone, which promotes increased insulin secretion and further weight gain.[38] Similarly, in the Zucker rat strain, increased vagal tone results in insulin hypersecretion that promotes weight gain.[39] Exogenous leptin administration above the leptin set-point re-establishes normal autonomic function, allowing for normal REE, increased physical activity, and weight loss due to lipolysis.

TWO FORMS OF CENTRAL NERVOUS SYSTEM LEPTIN RESISTANCE

Idiopathic obesity: 'functional' leptin resistance

This hypothetical CNS leptin set-point is dysfunctional in obesity; leptin levels are elevated, but do not trigger increased REE, lipolysis, or decreased food intake.[40] In the obese state, a higher level of leptin is required to signal the hypothalamus to maintain a normal REE. If energy intake declines, as occurs with dieting, leptin levels decline, triggering the starvation response; REE decreases, preventing further weight loss, with increased appetite, vagal activation, insulin hypersecretion, and increased energy storage. Exogenous leptin administration to obese individuals has only minor effects on weight loss because of CNS leptin resistance;[41] thus obesity is characterized as a functionally leptin-resistant state.[13]

Hypothalamic obesity: 'organic' leptin resistance

This phenomenon of CNS leptin resistance is recapitulated in the syndrome of hypothalamic obesity. Hypothalamic damage can be a sequel of cranial insult due to head trauma, posterior fossa brain tumors, surgery, or radiation.[42] A direct relationship between hypothalamic damage and BMI increase has been noted in survivors of childhood brain tumors.[43] Death of VMH neurons prevents normal leptin signal transduction, resulting in organic leptin resistance, which manifests as the starvation response. Decreased SNS tone[44] leads to decreased physical activity[45] and decreased energy expenditure. Conversely, increased vagal tone leads to increased pancreatic insulin

Figure 2 Central regulation of leptin signaling, autonomic innervation of adipocytes and β-cells, and the starvation response. (**A**) The arcuate nucleus transduces the peripheral leptin signal as one of sufficiency or deficiency. In leptin sufficiency, efferent fibers from the hypothalamus have synapses in the locus coeruleus, which stimulate the sympathetic nervous system. In leptin deficiency, efferent fibers from the hypothalamus stimulate the dorsal motor nucleus of the vagus nerve. (**B**) Autonomic innervation and hormonal stimulation of white adipose tissue. In leptin sufficiency, norepinephrine binds to the β_3-adrenergic receptor, which stimulates hormone-sensitive lipase, promoting lipolysis of stored triglyceride into free fatty acids. In leptin deficiency, vagus nerve mediated acetylcholine release activates the M1 receptor and increases adipose tissue insulin sensitivity (documented only in rats to date), promotes lipogenesis via uptake of glucose and free fatty acids, and promotes triglyceride uptake through activation of lipoprotein lipase. (**C**) Autonomic innervation and hormonal stimulation of β-cells. Glucose entering the cell is converted to glucose-6-phosphate by the enzyme glucokinase, generating ATP, which closes an ATP-dependent potassium channel and results in cell depolarization. A voltage-gated calcium channel opens, allowing intracellular calcium influx, which activates neurosecretory mechanisms leading to insulin vesicle exocytosis. In leptin sufficiency, norepinephrine binds to α_2-adrenoceptors on the β-cell membrane and stimulates inhibitory G proteins. Adenyl cyclase activity (and thus generation of its product, cyclic AMP) falls, which reduces protein kinase A levels and reduces insulin release. In leptin deficiency, vagus activation stimulates insulin secretion through three mechanisms.[28] First, acetylcholine binds to a M3 muscarinic receptor, opening a sodium channel, which augments the ATP-dependent cell depolarization, increases the calcium influx, and results in insulin vesicle exocytosis. Second, acetylcholine activates a pathway that increases protein kinase C levels, which also promotes insulin secretion. Third, vagus nerve fibers innervate L-cells of the small intestine, which secrete glucagon-like peptide 1, which activates protein kinase A and contributes to insulin-vesicle exocytosis. Octreotide binds to a somatostatin receptor on the β-cell that is coupled to the voltage-gated calcium channel. Octreotide, therefore, limits calcium influx and restricts the amount of insulin released in response to glucose.[11] Reproduced with permission from reference 28 © (2003) Springer Science and Business media. Abbreviations: + in circle and – in circle, positive and negative; α_2-AR, α_2-adrenergic receptor; β_3-AR, β_3-adrenergic receptor; AC, adenyl cyclase; ACh, acetylcholine; cAMP, cyclic AMP; Ca^{++}, calcium ions; DAG, diacylglycerol; DMV, dorsal motor nucleus of the vagus nerve; FFA, free fatty acids; G_i, inhibitory G protein; GK, glucokinase; GLP-1, glucagon-like peptide 1; GLP-1R, GLP-1 receptor; Glu-6-PO_4, glucose-6-phosphate; Glut4, glucose transporter 4; HSL, hormone-sensitive lipase; IML, intermediolateral cell column; IP_3, inositol triphosphate; K^+, potassium ions; K_{ATP}, ATP-dependent potassium channel; LC, locus coeruleus; LHA, lateral hypothalamic area; LPL, lipoprotein lipase; M1 and M3, muscarinic receptors; MARCKS, myristoylated alanine-rich protein kinase C substrate; Na^+, sodium ions; NE, norepinephrine; PIP_2, phosphatidylinositol pyrophosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PVN, paraventricular nucleus; SNS, sympathetic nervous system; SS5R, somatostatin receptor type 5; SUR, sufonylurea receptor; TG, triglyceride; V_{Ca}, voltage-gated calcium channel; VMH, ventromedial hypothalamus.

secretion[28] and increased adipocyte insulin sensitivity,[27] which promotes energy storage in adipose tissue. Patients manifest an extremely poor quality of life, with minimal physical activity; indeed parents complain that these are the most morbid sequelae such children experience.[42,45] Hypothalamic obesity is classically unresponsive to diet, exercise, and most pharmacologic manipulations.

PARADIGMS FOR IMPROVEMENT OF LEPTIN SENSITIVITY

If obesity is a state of CNS leptin resistance, then improving leptin sensitivity should result in weight loss and improved quality of life. Two strategies have so far been shown to improve leptin sensitivity in humans.

Forced weight loss

Rosenbaum *et al.*[46] employed inpatient energy restriction to generate 10% weight loss and induce the starvation response. In these individuals, leptin declined, and REE decreased, with commensurate decrease in serum T_3 levels. Exogenous administration of leptin in physiologic dosing to approximate the prestarvation leptin level resulted in further weight and fat decrease, along with return of REE and T_3 levels to the prestarvation state. In the prestarvation state, these individuals were resistant to physiologic concentrations of endogenous leptin, whereas in the weight-reduced state, they were responsive to the same concentrations of exogenously administered leptin—forced weight loss improved their inherent leptin sensitivity.

Insulin suppression

Hypothalamic obesity

Bray and Gallagher[47] posited that the weight gain in hypothalamic obesity was a result of the increased vagal tone after the VMH lesion, resulting in insulin hypersecretion that was evident on oral glucose tolerance testing (OGTT). My group hypothesized that suppression of β-cell insulin release should promote weight loss, despite the presence of 'organic' leptin resistance. We examined the effects of the somatostatin analog octreotide (an agonist of the somatostatin receptor type 5, which is present on β-cells and inhibits the voltage-gated calcium channel) (Figure 2C) in children with hypothalamic obesity. A pilot, open-label trial of subcutaneous octreotide 15 μg/kg per day for 6 months in eight patients[48] demonstrated a BMI loss commensurate with the degree of insulin suppression, along with decreased caloric intake, and subjective improvements in spontaneous physical activity and quality of life. A double-blind, placebo-controlled trial of octreotide in 20 individuals[49] resulted in insulin suppression and stabilization of BMI, decreased leptin levels, decreased caloric intake, increased spontaneous physical activity, and improvements in quality of life commensurate with the degree of insulin suppression. In other words, insulin suppression reversed the starvation response.

Adult obesity

In response to the success of octreotide in treating hypothalamic obesity, we then postulated that a subset of obese adults without CNS insult might also exhibit increased vagal tone and insulin hypersecretion, and might respond favorably to octreotide-LAR (long-acting release).[50] Treatment of 44 obese (mean BMI 44.1 kg/m^2) adults with octreotide-LAR (40 mg intramuscularly) at monthly intervals for 6 months resulted in significant weight (mean 12.6 kg) and BMI (mean 4.3 kg/m^2) loss in 8 individuals (the responders). These individuals manifested increased vagal tone, which correlated with insulin hypersecretion during the OGTT, as opposed to the 36 nonresponders who demonstrated insulin resistance. Indeed, octreotide-LAR suppressed insulin secretion only in the 8 responders.

Recalled caloric intake demonstrated an altered macronutrient preference, as responders selectively reduced their carbohydrate intake. In the responders, leptin concentration was reduced by 50%, but REE remained the same; so, when corrected for fat-free mass, REE increased. We used the change in REE:leptin ratio as a surrogate index of the change in leptin sensitivity in these individuals. Indeed, the REE:leptin ratio increased in those who lost weight. Linear regression analysis that compared the change in REE:leptin with the change in insulin response to OGTT demonstrated a significant negative correlation.[51] In other words, insulin suppression improved leptin sensitivity, as measured by this surrogate index. Notably, continued treatment of the responders for 1 year resulted in continued weight loss (mean 15.8 kg), with no ill effects. The beneficial effects of insulin suppression with octreotide-LAR, namely weight loss and improved quality of life, have been corroborated in a randomized, controlled trial of this agent in obese adults with insulin hypersecretion.[52]

Similarities between these paradigms

Forced weight loss improved leptin sensitivity, as measured by improvements in REE and thyroid hormone levels, in response to exogenous leptin. Insulin suppression using octreotide also improved leptin sensitivity, as measured by declining leptin concentrations with increased REE, allowing for weight loss and improved quality of life. Both strategies share at their core a reduction in systemic insulin concentrations. The similarity of outcome suggests that hyperinsulinemia may be a proximate cause of leptin resistance.

Molecular mechanisms of leptin resistance

The mechanism(s) of leptin resistance remain obscure. In rodents, diet-induced obesity (DIO) promotes defective leptin signal transduction, whether the leptin is administered peripherally or centrally;[53] however, DIO is also known to induce hyperinsulinemia.[54] Mouse models of improved leptin sensitivity with protection against weight gain have been demonstrated by knockout of the protein SOCS-3 (suppressor of cytokine signaling 3),[55] which inactivates the leptin receptor by dephosphorylating tyrosine 1138 (Figure 3).[56] Parenthetically, insulin induces SOCS-3,[57] which—as detailed below—could account for both insulin resistance and leptin resistance.

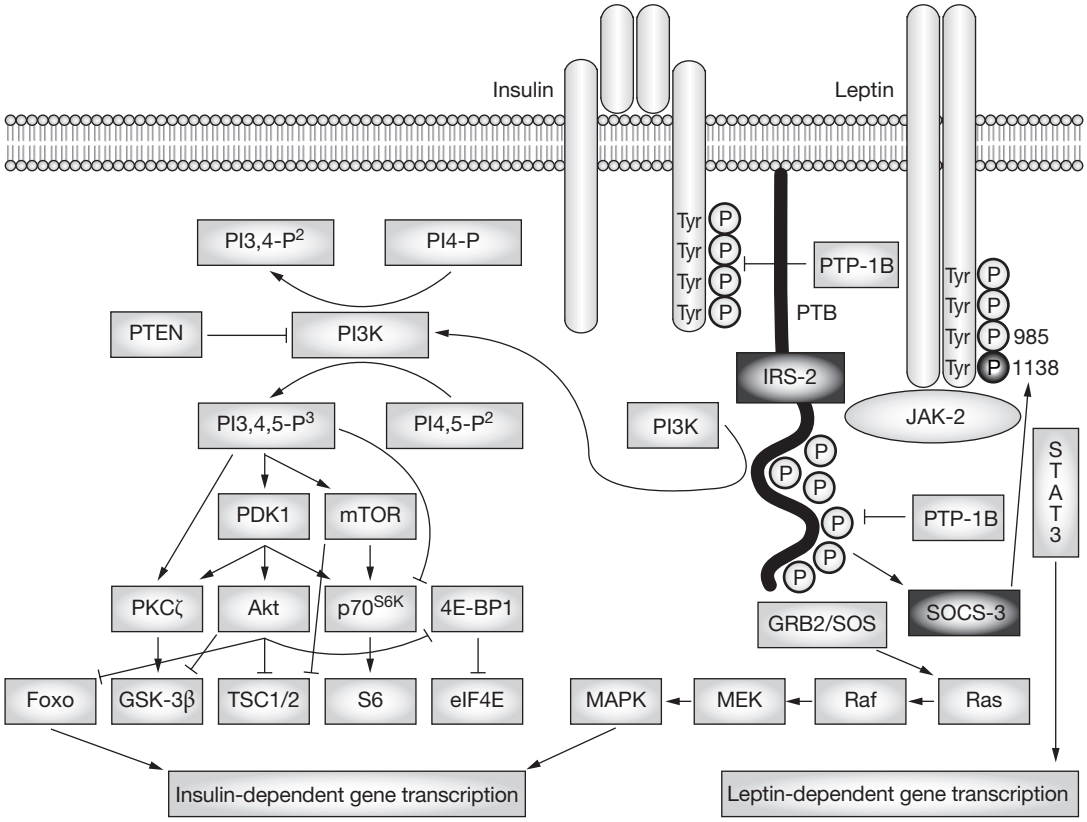

Figure 3 Overlap (depicted in black) between insulin and leptin signaling pathways in the ventromedial hypothalamic neuron. Insulin stimulates the insulin receptor substrate 2–phosphatidylinositol 3 kinase pathway, whereas leptin stimulates the Janus kinase 2–signal transduction and transcription 3 pathway; however, both the insulin receptor and the leptin receptor recruit the low-abundance-message second messenger insulin receptor substrate 2. Lack of available insulin receptor substrate 2 for the leptin receptor following hyperinsulinemia could result in defective leptin signal transduction. Alternatively, insulin induction of suppressor of cytokine signaling 3 could inactivate the leptin receptor, through dephosphorylation of tyrosine 1138.[80] Figure 3 was adapted by J Kushner and is modified with permission from reference 80 © (2005) Lippincott, Williams & Wilkins. Abbreviations: 4E-BP1, eukaryotic translation initiation factor 4E binding protein 1; Akt, protein kinase B; eIF4E, eukaryotic initiation factor 4E; Foxo, forkhead box proteins; GRB2, growth factor receptor-bound protein 2; GSK-3β, glycogen synthase kinase 3β; IRS-2, insulin receptor substrate 2; JAK-2, Janus kinase 2; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular-regulated kinase; mTOR, mammalian target of rapamycin; P, phosphate; $p70^{S6K}$, p70 S6 ribosomal kinase; PDK1, 3-phosphoinositide-dependent kinase 1; PI, phosphatidylinositol; PI3K, phosphatidylinositol 3 kinase; PKCζ, protein kinase Cζ; PTB, phosphotyrosine-binding domain; PTEN, phosphatase and tensin homolog; PTP-1B, protein-tyrosine phosphatase 1B; Raf, serine–threonine protein kinase; Ras; activator of Raf; S6, 40S ribosomal protein S6; SOCS-3, suppressor of cytokine signaling 3; SOS, son of sevenless; STAT3, signal transduction and transactivation 3; TSC, tumor suppressor C; Tyr, tyrosine.

CROSSTALK BETWEEN INSULIN AND LEPTIN

Acute insulin and leptin effects overlap

Insulin and leptin parallel one another's short-term effects in the CNS.[22] Both hormones are secreted during periods of energy sufficiency or excess, their receptors co-localize to the same VMH neurons, and both have similarly anorexigenic effects when administered directly into cerebrospinal fluid. Their similarities of action suggest they act as dual barometers of energy stores; insulin levels reflect short-term changes in energy intake, whereas leptin levels reflect energy balance over a longer period of time. Obesity is, however, a state in which the negative feedback that should result from chronic CNS exposure to

insulin and leptin is ineffective; appetite remains uncurbed and weight accrues despite adequate energy stores.

Chronic insulin antagonizes leptin signaling

Decreased central nervous system leptin transport

The observation that intracerebroventricular leptin is more effective than systemic leptin administration suggests that leptin resistance could be due to limited availability of the hormone in the CNS.[58] Indeed, low levels of leptin in cerebrospinal fluid have been documented in rodent models[59] and in human obesity.[60] Leptin is transported into the CNS via a transporter expressed in brain vasculature. This transport is decreased in obesity;[58] however, insensitivity to the behavioral effects of intracerebroventricular insulin and leptin has also been found in the chronically hyperinsulinemic obese Zucker rat strain, and also in DIO.[61] Inadequate transport into the CNS does not fully explain the leptin resistance seen in obesity, but may be a contributing factor.

Decreased neuronal leptin signal transduction

Although insulin and leptin bind to separate receptors, they share the IRS-2–PI3K signal transduction pathway.[18,22] Intracellular signaling by the leptin receptor is usually achieved through the Janus kinase 2–signal transduction and transactivation 3 (JAK-2–STAT3) pathway (Figure 3). Leptin's ability to activate STAT3 in hypothalamic neurons is reduced in DIO, which also induces hyperinsulinemia.[53] SOCS-3 and protein tyrosine phosphatase 1B are two proteins that regulate leptin sensitivity;[62] decreased expression (or knockout) of their respective genes enhances leptin sensitivity and gives rise to phenotypically lean mice. Studies of DIO and age-associated obesity suggest that SOCS-3 expression is affected in these states.[63] Insulin induces SOCS-3,[57] which then inactivates signal transduction from the insulin receptor, and inactivates the leptin receptor (by dephosphorylating tyrosine 1138).[56]

In addition, both insulin and leptin receptors use the low-abundance-message second-messenger IRS-2, in order to facilitate PI3K activity. The role of IRS-2 in leptin resistance is, however, controversial. One study suggested that knockout of IRS-2 in hypothalamic neurons promoted obesity and insulin resistance, and prevented leptin signal transduction, conferring a leptin-resistant state;[20] another study of IRS-2 knockout shows similar effects on promoting obesity, but with maintenance of leptin sensitivity.[21] Although not yet confirmed, these data suggest that hyperinsulinemia and resultant CNS insulin resistance may be a proximate cause of leptin resistance that promotes weight gain.

Adaptive advantage for insulin's role as a leptin antagonist

Teleologically, what could be the biological advantage for antagonism of leptin's actions by insulin in the obese state? Reversible antagonism of leptin's actions would be desirable in physiological phenomena in which rapid weight gain is essential. Similar conditions can be found during both puberty and pregnancy; two processes essential for reproduction. If leptin signaling could not be modulated, the weight accrual necessary for reproductive competence would be compromised. Indeed, both puberty and pregnancy are hyperinsulinemic and insulin-resistant states, because of the effects of sex hormones and growth hormone on insulin sensitivity in target tissues,[64] and of reciprocal increases in insulin release.

In both of these physiologic states, leptin levels increase sharply; postpuberty or postpartum, insulin levels fall, weight stabilizes or is lost, and leptin levels return toward the baseline state.[65,66] Insulin antagonism of leptin signal transduction is probably an integral control mechanism to ensure reproductive competence. In maladaptive conditions, however, when insulin rises chronically either through pancreatic hypersecretion (as is seen in hypothalamic obesity), or through insulin resistance (as is seen in certain ethnic populations, or in DIO in rodents), leptin signal transduction is impeded, and the obese state is either maintained or promulgated.

THE HEDONIC PATHWAY OF FOOD REWARD

The homeostatic pathway is not the only central arbiter of energy balance. Complementary to the ability of both insulin and leptin to alter feeding behavior, these hormones also modify the 'hedonic pathway' (which regulates pleasurable and motivating responses to stimuli). This pathway localizes to the ventral tegmental area (VTA) and the nucleus accumbens (NA), with inputs from various components of the limbic system, including the striatum, amygdala, hypothalamus and hippocampus. The hedonic pathway responds to drugs of abuse, such as nicotine and morphine. Food intake is responsive

to activation of the hedonic pathway; for example, administration of morphine to the NA increases food intake in a dose-dependent fashion.[67] Dopaminergic perikarya terminals project from the VTA to the NA, which mediates the rewarding and reinforcing properties of various stimuli, including food and addictive drugs. The VTA initiates feeding on the basis of palatability rather than energy need. Stimulation of this area triggers feeding behavior in rats that have already been fed, provided they are given a palatable food.

Insulin and leptin alter VTA–NA dopamine neurotransmission

Leptin and insulin receptors are expressed in the VTA, and both hormones have been implicated in modulating rewarding responses to food and other pleasurable stimuli. For instance, fasting or food restriction (during which insulin and leptin levels are low) increase the addictive properties of drugs of abuse, whereas intracerebroventricular leptin can reverse these effects.[68] In rodent models of addiction, increased addictive behavior, and pleasurable response from a food reward, as measured by dopamine release, is greater after food deprivation.[69] Obesity also results in decreased density of D_2 dopamine receptors as measured by PET scanning.[70]

In the short term, insulin increases expression and activity of the dopamine transporter, which clears and removes dopamine from the synapse; thus, acute insulin exposure blunts the reward of food in rats.[71] D_2-receptor antagonists and insulin act additively to acutely decrease the rewarding response to a palatable sucrose solution; furthermore, insulin seems to inhibit the ability of VTA-agonists (e.g. opioids) to increase intake of sucrose.[72] Finally, insulin blocks the ability of rats to form a conditioned place-preference association to a palatable food.[73]

Hyperinsulinemia could increase the reward derived from food

Insulin resistance at the VTA might contribute to obesity by preventing dopamine clearance from the NA, thus increasing pleasure derived from food in situations where energy stores are replete. CNS insulin resistance sets the stage for unchecked caloric intake in the face of positive energy balance, as evidenced experimentally by brain-specific insulin receptor knockout mice.[19] By altering hedonic responses to food, insulin resistance at the VTA may drive excessive energy intake.

WHERE DID THE HYPERINSULINEMIA COME FROM?

Hyperinsulinemia in the pediatric age group reflects genetic, epigenetic, and environmental origins. Firstly, children from certain ethnic groups have been identified to possess altered insulin dynamics compared with those of white, European ancestry, even before the development of obesity, which might predispose them to increased weight gain.[74] We have described increased insulin secretion among obese African Americans that is not explained by their obesity.[75] Secondly, the 'fetal origins of adult disease' hypothesis proposes that individuals who are either small-for-gestational-age or large-for-gestational-age at birth are prone to obesity and the metabolic syndrome in adulthood;[76] hyperinsulinemia and insulin resistance are present in both these birthweight states, and worsen with time.[77] Premature infants also develop insulin resistance in later life.[78] Indeed, low-birthweight babies who demonstrate the most rapid 'catch-up' growth after birth are those most likely to become obese.[79] Lastly, our current Western diet is highly insulinogenic, as demonstrated by its increased energy density, high fat content, high glycemic index, increased fructose composition, decreased fiber, and decreased dairy content.[80]

CONCLUSIONS: REINTERPRETING THE FIRST LAW OF THERMODYNAMICS

In this review, the CNS mechanisms underlying weight gain are described. Within the afferent arm of the homeostatic pathway of energy balance, leptin and insulin are often equated because of their short-term effects; however, the hyperinsulinemic state interferes with leptin signal transduction, as insulin acts as an endogenous leptin antagonist. This interference promotes leptin resistance, which should decrease SNS activity to reduce REE, and increase vagal activity to promote energy storage; except that, of course, the obese subject—of necessity—increases caloric intake, which raises their leptin concentration above the level at which leptin resistance occurs, so as to maintain normal energy expenditure and quality of life. The insulin resistance that is a characteristic of the obese state promotes further leptin resistance. Hyperinsulinemia also decreases dopamine clearance and uptake in the hedonic pathway, which promotes an increased reward of food that causes increased food intake. This effect also maintains the hyperinsulinemic state.

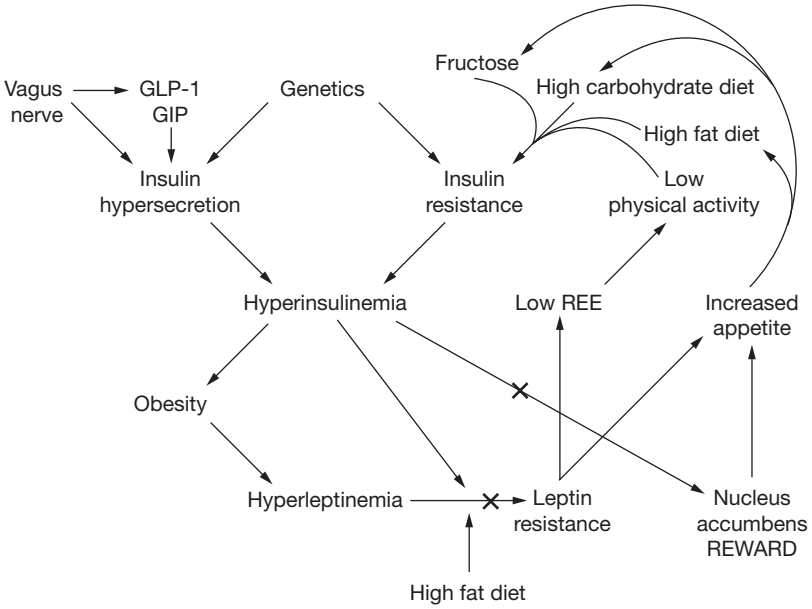

Figure 4 Insulin, leptin, reward and obesity. An algorithm describing the role of hyperinsulinemia in the dysfunction of the energy balance pathway. Various factors can lead to hyperinsulinemia, including vagus nerve mediated insulin hypersecretion, or hepatic and/or skeletal muscle insulin resistance. Hyperinsulinemia interferes with leptin signal transduction in the hypothalamus, promoting leptin resistance. This interference causes resting energy expenditure to decrease and appetite to increase, promoting further weight gain. In addition, hyperinsulinemia prevents dopamine reuptake at the nucleus accumbens, thus fostering increased reward associated with eating food, which promotes increased caloric intake. Hyperinsulinemia, therefore, converts the homeostatic and hedonic pathways from traditional negative feedback to feed-forward mechanisms.[80] Reproduced with permission from reference 80 © (2005) Lippincott, Williams & Wilkins. Abbreviations: GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; REE, resting energy expenditure; X, inhibition.

The phenomenon of hyperinsulinemia turns two neuroendocrine negative feedback systems into feed-forward systems (or 'vicious cycle', in which the product stimulates further substrate production or action, rather than inhibiting it). Hyperinsulinemia promotes increased energy intake and decreased energy expenditure (Figure 4). Externally, this manifests as 'gluttony and sloth', but it is biochemically driven. In this paradigm, the First Law of Thermodynamics can be expressed so that the weight gain is primary, and the resulting behaviors are secondary: "If you store it (obligate weight gain occurs in response to hyperinsulinemia), and you expect to burn it (maintain normal REE and quality of life), then you must eat it (food intake increases)".

Although there are numerous contributors to hyperinsulinemia, our current food and activity environment is the most important, and the most amenable to change; however, it will take acknowledgment of the concepts of biological susceptibility and societal accountability, and de-emphasis of the concept of personal responsibility, to make a difference in the lives of children.

KEY POINTS

- Behavior has biochemical underpinnings, particularly the pathologic behaviors in disease states
- Obesity is characterized by hyperinsulinemia and leptin resistance
- In the long term, insulin functions as an endogenous leptin antagonist; it interferes with leptin signal transduction resulting in increased food intake and decreased physical activity
- Chronic hyperinsulinemia interferes with satiety by preventing extinction of the hedonic response to food
- Hyperinsulinemia has genetic, epigenetic, and environmental inputs

References

1 Ogden CL *et al*. (2002) Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA* **288:** 1728–1732
2 Hill JO *et al*. (2003) Obesity and the environment: where do we go from here? *Science* **299:** 853–855
3 Ebbeling CB *et al*. (2002) Childhood obesity: public-health crisis, common sense cure. *Lancet* **360:** 473–482
4 Troiano RP *et al*. (2000) Energy and fat intakes of children and adolescents in the United States: data from the National Health and Nutrition Examination Surveys. *Am J Clin Nutr* **72 (Suppl):** 1343S–1353S
5 Kimm SYS *et al*. (2002) Decline in physical activity in black girls and white girls in adolescence. *N Engl J Med* **347:** 709–715
6 Schwimmer JB *et al*. (2003) Health-related quality of life of severely obese children and adolescents. *JAMA* **289:** 1813–1819
7 Epstein LH *et al*. (2001) Behavioral therapy in the treatment of pediatric obesity. *Pediatr Clin North Am* **48:** 981–993
8 Ritchie L *et al*. (2001) Pediatric overweight: a review of the literature [http://www.cnr.berkeley.edu/cwh/PDFs/Full_COPI_secure.pdf] (accessed 17 May 2006)
9 Lustig RH (2001) The neuroendocrinology of childhood obesity. *Pediatr Clin North Am* **48:** 909–930
10 Balthasar N *et al*. (2005) Divergence of melanocortin pathways in the control of food intake and energy expenditure. *Cell* **123:** 493–505
11 Lustig RH The efferent arm of the energy balance regulatory pathway: neuroendocrinology and pathology. In *Obesity and Energy Metabolism: Research and Clinical Applications* (Ed Donahoue PA) New Jersey: Humana, in press
12 Porte D *et al*. (2005) Insulin signaling in the central nervous system: a critical role in metabolic homeostasis and disease from *C. elegans* to humans. *Diabetes* **54:** 1264–1276
13 Flier JS (1998) What's in a name? In search of leptin's physiologic role. *J Clin Endocrinol Metab* **83:** 1407–1413

14 Mark AL *et al*. (2003) A leptin-sympathetic-leptin feedback loop: potential implications for regulation of arterial pressure and body fat. *Acta Physiol Scand* **177:** 345–349
15 Baskin DG *et al*. (1988) Insulin and insulin-like growth factors in the CNS. *Trends Neurosci* **11:** 107–111
16 Schwartz MW *et al*. (1990) Insulin binding to brain capillaries is reduced in genetically obese, hyperinsulinemic Zucker rats. *Peptides* **11:** 467–472
17 Muntzel MS *et al*. (1994) Intracerebroventricular insulin produces nonuniform regional increases in sympathetic nerve activity. *Am J Physiol* **267 (Pt 2):** R1350–R1355
18 Niswender KD *et al*. (2001) Intracellular signalling. Key enzyme in leptin-induced anorexia. *Nature* **413:** 794–795
19 Brüning JC *et al*. (2000) Role of brain insulin receptor in control of body weight and reproduction. *Science* **289:** 2122–2125
20 Kubota N *et al*. (2004) Insulin receptor substrate 2 plays a crucial role in β cells and the hypothalamus. *J Clin Invest* **114:** 917–927
21 Choudhury AI *et al*. (2005) The role of insulin receptor substrate 2 in hypothalamic and beta cell function. *J Clin Invest* **115:** 940–950
22 Niswender KD and Schwartz MW (2003) Insulin and leptin revisited: adiposity signals with overlapping physiological and intracellular signaling capabilities. *Front Neuroendocrinol* **24:** 1–10
23 Lowell BB and Spiegelman BM (2000) Towards a molecular understanding of adaptive thermogenesis. *Nature* **404:** 652–660
24 Collins S *et al*. (1996) Role of leptin in fat regulation [letter]. *Nature* **380:** 677
25 Haynes WG *et al*. (1997) Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Invest* **100:** 270–278
26 Blaak EE *et al*. (1993) Adrenoceptor subtypes mediating catecholamine-induced thermogenesis in man. *Int J Obes Relat Metab Disord* **17 (Suppl 3):** S78–S81
27 Kreier F *et al*. (2002) Selective parasympathetic innervation of subcutaneous and intra-abdominal fat-functional implications. *J Clin Invest* **110:** 1243–1250
28 Lustig RH (2003) Autonomic dysfunction of the β-cell and the pathogenesis of obesity. *Rev Endocr Metab Disord* **4:** 23–32
29 Yamada M *et al*. (2001) Mice lacking the M3 muscarinic acetylcholine receptor are hypophagic and lean. *Nature* **410:** 207–212
30 Bray GA and Greenway FL (1999) Current and potential drugs for treatment of obesity. *Endocr Rev* **20:** 805–875
31 Leibel RL *et al*. (1995) Changes in energy expenditure resulting from altered body weight. *N Engl J Med* **332:** 621–628
32 Rosenbaum M *et al*. (1997) Effects of weight change on plasma leptin concentrations and energy expenditure. *J Clin Endocrinol Metab* **82:** 3647–3654
33 Rosenbaum M *et al*. (2003) Effects of experimental weight perturbation on skeletal muscle work efficiency in human subjects. *Am J Physiol Regul Integr Comp Physiol* **285:** R183–R192
34 Smit HJ *et al*. (2004) Mood and cognitive performance effects of "energy" drink constituents: caffeine, glucose, and carbonation. *Nutr Neurosci* **7:** 127–139
35 Belza A and Jessen AB (2005) Bioactive food stimulants of sympathetic activity: effect on 24-h energy expenditure and fat oxidation. *Eur J Clin Nutr* **59:** 733–741
36 Boden G *et al*. (1996) Effect of fasting on serum leptin in normal human subjects. *J Clin Endocrinol Metab* **81:** 454–458
37 Aronne LJ *et al*. (1995) Autonomic nervous system activity in weight gain and weight loss. *Am J Physiol* **269:** R222–R225
38 Farooqi IS *et al*. (2002) Beneficial effects of leptin on obesity, T-cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest* **110:** 1093–1103
39 Lee HC *et al*. (1989) Direct effect of CNS on insulin hypersecretion in obese Zucker rats: involvement of vagus nerve. *Am J Physiol* **256:** E439–E444
40 van Dijk G *et al*. (2005) Reduced anorexigenic efficacy of leptin, but not of the melanocortin receptor agonist melanotan-II, predicts diet-induced obesity in rats. *Endocrinology* **146:** 5247–5256
41 Heymsfield SB *et al*. (1999) Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA* **282:** 1568–1575
42 Poretti A *et al*. (2004) Outcome of craniopharyngioma in children: long-term complications and quality of life. *Dev Med Child Neurol* **46:** 220–229
43 Lustig RH *et al*. (2003) Risk factors for the development of obesity in children surviving brain tumors. *J Clin Endocrinol Metab* **88:** 611–616
44 Schofl C *et al*. (2002) Sympathoadrenal counterregulation in patients with hypothalamic craniopharyngioma. *J Clin Endocrinol Metab* **87:** 624–629
45 Harz KJ *et al*. (2003) Obesity in patients with craniopharyngioma: assessment of food intake and movement counts indicating physical activity. *J Clin Endocrinol Metab* **88:** 5227–5231
46 Rosenbaum M *et al*. (2002) Low dose leptin administration reverses effects of sustained weight reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab* **87:** 2391–2394
47 Bray GA and Gallagher TF (1975) Manifestations of hypothalamic obesity in man: a comprehensive investigation of eight patients and a review of the literature. *Medicine (Baltimore)* **54:** 301–333
48 Lustig RH *et al*. (1999) Hypothalamic obesity in children caused by cranial insult: altered glucose and insulin dynamics, and reversal by a somatostatin agonist. *J Pediatr* **135:** 162–168
49 Lustig RH *et al*. (2003) Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* **88:** 2586–2592
50 Velasquez-Mieyer PA *et al*. (2003) Suppression of insulin secretion promotes weight loss and alters macronutrient preference in a subset of obese adults. *Int J Obesity* **27:** 219–226
51 Lustig RH *et al*. (2004) Obesity, leptin resistance, and the effects of insulin suppression. *Int J Obesity* **28:** 1344–1348
52 Lustig RH *et al*. (2006) A multicenter, randomized, double-blind, placebo-controlled, dose-finding trial of a long-acting formulation of octreotide in promoting weight loss in obese adults with insulin hypersecretion. *Int J Obes* **30:** 331–341
53 El-Haschimi K *et al*. (2000) Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. *J Clin Invest* **105:** 1827–1832
54 Clegg DJ *et al*. (2005) Reduced anorexic effects of insulin in obesity-prone rats fed a moderate fat diet. *Am J Physiol Regul Integr Comp Physiol* **288:** R981–R986
55 Mori H *et al*. (2004) Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. *Nat Med* **10:** 739–743
56 Munzberg H and Myers MG (2005) Molecular and anatomical determinants of central leptin resistance. *Nat Neurosci* **8:** 566–570

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57 Emanuelli B *et al*. (2000) SOCS-3 is an insulin-induced negative regulator of insulin signaling. *J Biol Chem* **275:** 15985–15991
58 Banks W *et al*. (1999) Impaired transport of leptin across the blood-brain barrier in obesity. *Peptides* **20:** 1341–1345
59 Ishihara Y *et al*. (2004) Effects of diet and time of the day on serum and CSF leptin levels in Osborne-Mendel and S5B/Pl rats. *Obes Res* **12:** 1067–1076
60 Nam SY *et al*. (2001) Cerebrospinal fluid and plasma concentrations of leptin, NPY, and α-MSH in obese women and their relationship to negative energy balance. *J Clin Endocrinol Metab* **86:** 4849–4853
61 Figlewicz DP *et al*. (1996) Review article: endocrine regulation of food intake and body weight. *J Lab Clin Med* **127:** 328–332
62 Zabolotny JM *et al*. (2002) PTP1B regulates leptin signal transduction *in vivo. Dev Cell* **2:** 489–495
63 Flier JS (2004) Obesity wars: molecular progress confronts an expanding epidemic. *Cell* **116:** 337–350
64 Li HJ *et al*. (2005) A twin study for serum leptin, soluble leptin receptor, and free insulin-like growth factor-1 in pubertal females. *J Clin Endocrinol Metab* **90:** 3659–3664
65 McLachlan KA *et al*. (2006) Do adiponectin, TNFα, leptin, and CRP relate to insulin resistance in pregnancy? Studies in women with and without gestational diabetes, during and after pregnancy. *Diab Metab Res Rev* **22:** 131–138
66 Castracane VD *et al*. (2005) Serum leptin in nonpregnant and pregnant women and in old and new world nonhuman primates. *Exp Biol Med* **230:** 251–254
67 Kelley AE *et al*. (2002) Opioid modulation of taste hedonics within the ventral striatum. *Physiol Behav* **76:** 365–377
68 Shalev U *et al*. (2001) Leptin attenuates food deprivation-induced relapse to heroin seeking. *J Neurosci* **21:** RC129
69 Carr KD *et al*. (2003) Evidence of increased dopamine receptor signaling in food-restricted rats. *Neuroscience* **119:** 1157–1167
70 Wang GJ *et al*. (2001) Brain dopamine and obesity. *Lancet* **357:** 354–357
71 Figlewicz DP *et al*. (1994) Intraventricular insulin increases dopaminergic transporter mRNA in rat VTA/substantia nigra. *Brain Res* **644:** 331–334
72 Sipols AJ *et al*. (2002) Intraventricular insulin decreases kappa opioid-mediated sucrose intake in rats. *Peptides* **23:** 2181–2187
73 Figlewicz DP (2003) Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. *Am J Phyisol Regul Integ Comp Physiol* **284:** R882–R892
74 Arslanian SA *et al*. (2002) Hyperinsulinemia in African-American children. Decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity. *Diabetes* **51:** 3014–3019
75 Preeyasombat C *et al*. (2005) Racial and etiopathologic dichotomies in insulin secretion and resistance in obese children. *J Pediatr* **146:** 474–481
76 Stocker CJ *et al*. (2005) Fetal origins of insulin resistance and obesity. *Proc Nutr Soc* **64:** 143–151
77 Yajnik CS *et al*. (2002) Adiposity and hyperinsulinemia in Indians are present at birth. *J Clin Endocrinol Metab* **87:** 5575–5580
78 Hofman PL *et al*. (2004) Premature birth and later insulin resistance. *N Engl J Med* **351:** 2179–2186
79 Cettour-Rose P *et al*. (2005) Redistribution of glucose from skeletal muscle to adipose tissue during catch-up fat: a link between catch-up growth and later metabolic syndrome. *Diabetes* **54:** 751–756
80 Isganaitis E and Lustig RH (2005) Fast food, central nervous system insulin resistance, and obesity. *Arterioscler Thromb Vasc Biol* **25:** 2451–2462