2 The Neuroendocrine Control of Energy Balance

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INTRODUCTION

When discussing the causes of obesity, it is easy to point fingers at the individual. "Gluttony" and "sloth" after all are two of the seven "deadly sins." Obese adults and their children are assumed to have "free choice" with regard to food intake and energy expenditure and are therefore "responsible" for their metabolic "fates" *(1)*. But no child chooses to become obese; indeed the quality of life of an obese child is similar to that of children receiving cancer chemotherapy *(2)*. Furthermore, the striking increases in obesity prevalence in 2- to 5-year-old children *(3)* suggest that there are other explanations for the obesity epidemic. Here I explore the biochemical determinants that control energy balance and argue that difficulties in achieving and/or maintaining weight loss reflect the potency of central reinforcement systems, the effects of stress, and the resilience of the body's adaptive responses.

The discovery of leptin in 1994 *(4)* revealed a complex neuroendocrine axis regulating energy balance. Much of what we know about energy balance is derived from studies of animal models, but clinical studies provide invaluable insights.
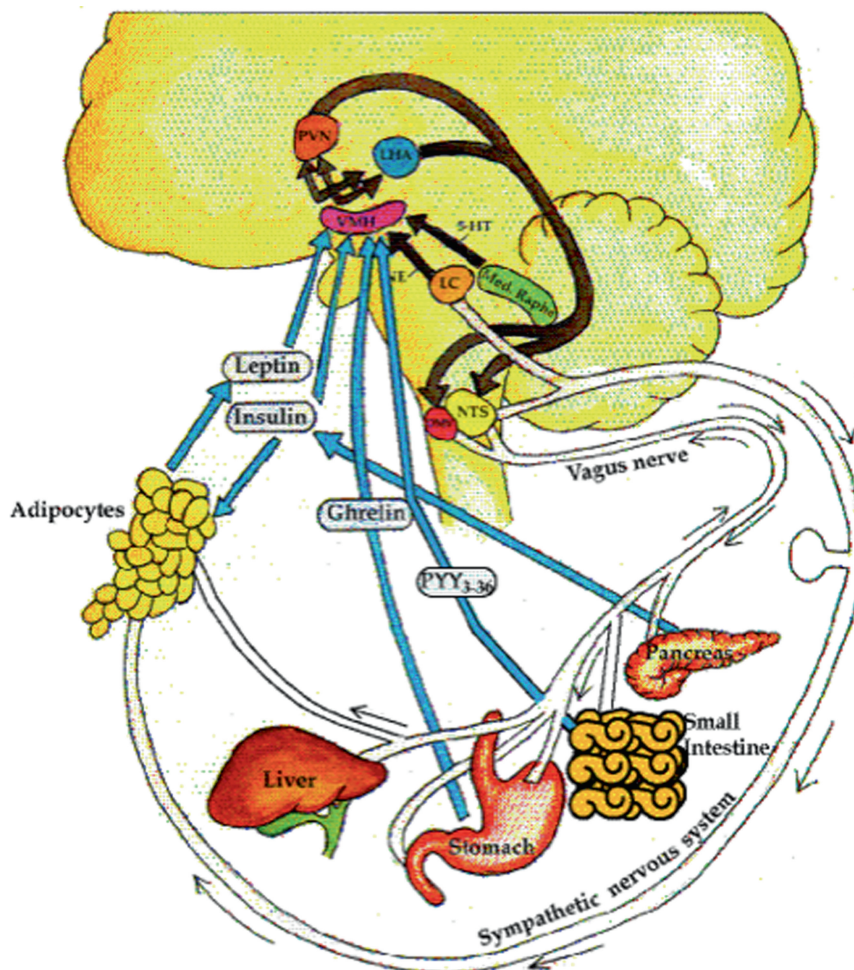
Fig. 1. The homeostatic pathway of energy balance. Afferent (*blue*), central (*black*), and efferent (*white*) pathways are delineated. The hormones insulin, leptin, ghrelin, and peptide YY$_{(3–36)}$ (PYY$_{3–36}$) provide afferent information to the ventromedial hypothalamus regarding short-term energy 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 lead to efferent output via the locus coeruleus and the nucleus tractus solitarius, which activate the sympathetic nervous system, causing the adipocyte to undergo lipolysis; or the dorsal motor nucleus of the vagus, which activates the vagus nerve to store energy, both by increasing pancreatic insulin secretion and (in rodents) by increasing adipose tissue sensitivity to insulin. 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; VMH, ventromedial hypothalamus. From Lustig *(21)*. (Courtesy of Nature Publishing Group, with permission.)

The neuroendocrine axis is composed of three arms (Fig. 1). The first is the *afferent arm*, which conveys peripheral information on hunger and peripheral metabolism (in the form of hormonal and neural inputs) to the hypothalamus. The second is a *central processing unit*, consisting of various areas within the hypothalamus. These include (a) the ventromedial hypothalamus (VMH; consisting of the ventromedial (VMN) and arcuate (ARC) nuclei), which integrates afferent peripheral signals as well as other central stimuli, and (b) the paraventricular nuclei (PVN) and lateral hypothalamic area (LHA),

which serve as a gated neurotransmitter system to alter neural signals for changes in feeding and energy expenditure. Other brain areas serve as neuromodulators of this system. The third component is an *efferent arm* of autonomic effectors with origins in the locus coeruleus (LC) and dorsal motor nucleus of the vagus (DMV), which regulate energy intake, expenditure, and storage *(5,6)*. Anatomic disruptions or genetic or metabolic alterations of either the afferent, central processing, or efferent arms can alter energy intake or expenditure, leading to either obesity or cachexia.

There are three primary stimuli to eat: *hunger, reward,* and *stress*. While each of these internal phenomena infer altered behavior, each is actually mediated through a complex cascade of biochemicals that perturb the negative feedback pathway of energy balance and "drive" food intake in stereotypical patterns.

COMPONENTS OF THE AFFERENT SYSTEM

Alimentary Afferents That Promote Hunger

The afferent vagus: The vagus nerve is the primary neural connection between the brain and the gut. The afferent vagus nerve conveys information regarding mechanical stretch of the stomach and duodenum and feelings of gastric fullness to the nucleus tractus solitarius (NTS) *(7)*. Of note, the effects of alimentary neuropeptides (below) on hunger and satiety are obviated by concomitant vagotomy, implicating the afferent vagus as the primary mediator of alimentary energy balance signals *(8–10)*.

Ghrelin: Ghrelin, an octanoylated 28-amino acid peptide, was discovered serendipitously during a search for the endogenous ligand of the growth hormone secretagogue receptor (GHS-R) *(11)*. Ghrelin induces GH release through stimulation of the pituitary GHS-R. The endogenous secretion of ghrelin from the stomach is high during fasting and decreased by nutrient administration; volumetric stretching of the stomach wall has no effect. In addition to interacting with pituitary GHS receptors, ghrelin binds to the GHS-R in the VMH and thereby increases hunger, food intake, and fat deposition *(12,13)*. Ghrelin also increases the respiratory quotient (RQ) in rats, suggesting a reduction of fat oxidation. Ghrelin appears to link the lipolytic effect of GH with hunger signals and is probably important in the acute response to fasting. In humans, ghrelin levels rise with increasing subjective hunger and peak at the time of voluntary food consumption *(14)*, suggesting that ghrelin acts on the VMH to trigger meal initiation. Ghrelin infusion increases food intake in humans *(15)*. However, plasma ghrelin levels are low in most obese individuals and increase with fasting *(16)*, suggesting that ghrelin is a response to, rather than a cause of, obesity. The Prader–Willi syndrome, an obesity disorder associated with hyperghrelinemia, may be a unique exception (see Chapter 4 by Haqq, this volume).

Alimentary Afferents That Promote Satiety

Peptide YY$_{3–36}$ (PYY$_{3–36}$): PYY$_{3–36}$ is a gastrointestinal signal to control meal volume *(17)*. This peptide fragment is secreted by intestinal L-cells following exposure to nutrients; PYY crosses the blood–brain barrier and binds to the Y$_2$ receptor in the VMH. Activation of this receptor reduces neuropeptide Y (NPY) mRNA in neurons of the orexigenic arm of the central processing unit (below). In non-obese humans, infusion of PYY$_{3–36}$ during a 12-h period decreased the total volume of food ingested from 2,200 to 1,500 k/cal but had no effect on food ingested during the next 12-h interval *(17)*. Although the pharmacology of this peptide is being elucidated, and agonists are being developed, its specific role in obesity is not yet known.

Glucagon-like peptide-1 (GLP-1): Those same intestinal L-cells produce GLP-1 through post-translational processing of the preproglucagon molecule. Two equipotent forms of GLP-1 are generated: a glycine-extended form GLP-1$_{7–37}$ and the amidated peptide GLP-1$_{7–36}$ amide *(18)*. GLP-1 acts on the stomach to inhibit gastric emptying; this increases the time available for absorption of a meal. GLP-1 also activates its receptor on β-cells to stimulate cAMP production, protein
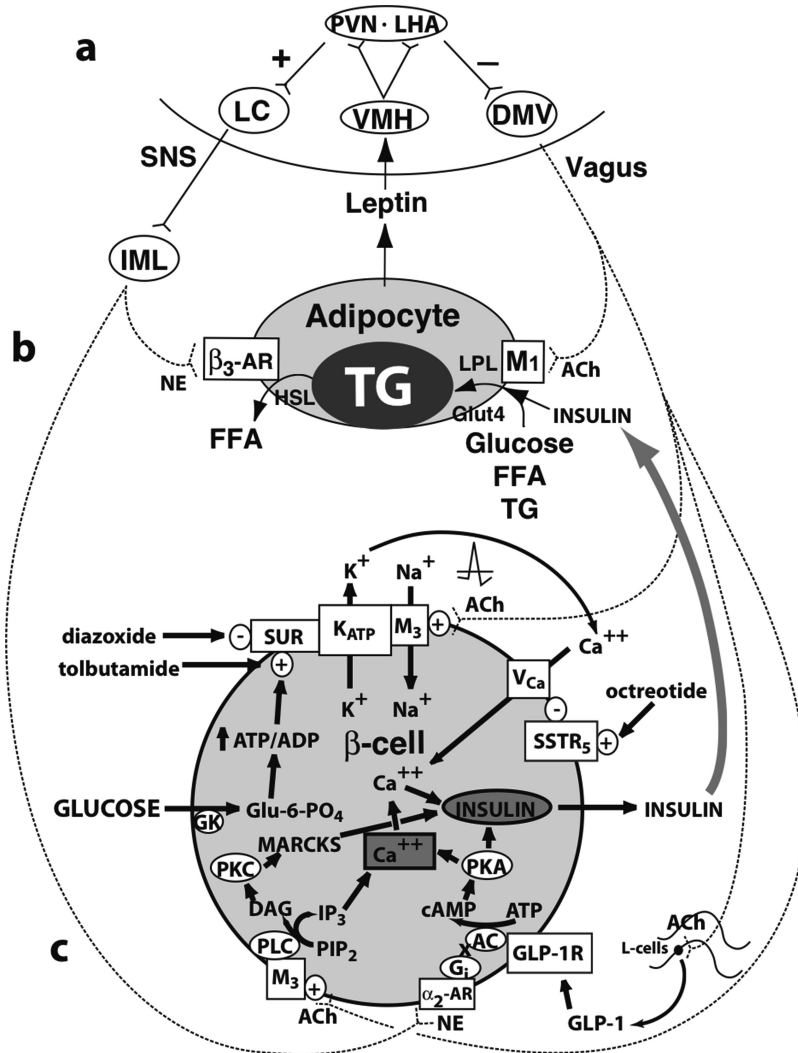
Fig. 2. Central regulation of leptin signaling, autonomic innervation of the adipocyte and β-cell, and the starvation response. (**a**) The arcuate nucleus transduces the peripheral leptin signal as one of sufficiency or deficiency. In leptin sufficiency, efferents from the hypothalamus synapse in the locus coeruleus, which stimulates the sympathetic nervous system. In leptin deficiency or resistance, efferents from the hypothalamus stimulate the dorsal motor nucleus of the vagus. (**b**) Autonomic innervation and hormonal stimulation of white adipose tissue. In leptin sufficiency, norepinephrine binds to the β₃-adrenergic receptor, which stimulates hormone-sensitive lipase, promoting lipolysis of stored triglyceride into free fatty acids. In leptin deficiency or resistance, vagal acetylcholine increases adipose tissue insulin sensitivity (documented only in rats to date), promotes uptake of glucose and free fatty acids for lipogenesis, and promotes triglyceride uptake through activation of lipoprotein lipase. (**c**) Autonomic innervation and hormonal stimulation of the β-cell. Glucose entering the cell is converted to glucose-6-phosphate by the enzyme glucokinase, generating ATP, which closes an ATP-dependent potassium channel, resulting in cell depolarization. A voltage-gated calcium channel opens, allowing for intracellular calcium influx, which activates neurosecretory mechanisms leading to insulin vesicular exocytosis. In leptin sufficiency, norepinephrine binds to α₂-adrenoceptors on the β-cell membrane to stimulate inhibitory G proteins, decrease adenyl cyclase and its product cAMP, and thereby reduce protein kinase A levels and insulin release. In leptin deficiency or resistance, the vagus stimulates insulin secretion *(105)*. Octreotide binds to a somatostatin receptor on the β-cell, which is coupled to the voltage-gated calcium channel, limiting calcium influx and the amount of insulin released in response to glucose (reprinted with kind permission of Springer Science and Business media). α₂-AR, α₂-adrenergic receptor; β₃-AR, β₃-adrenergic receptor; AC, adenyl cyclase;

kinase A activation, and insulin secretion (Fig. 2) and thereby improves glucose tolerance in patients with type 2 diabetes. GLP-1 also stimulates β-cell replication and increases β-cell mass *(19)*. Lastly, GLP-1 reduces food intake by reducing gastric emptying and corticotropin-releasing hormone (CRH) signaling in the PVN and increasing leptin signaling in the VMH *(20)*.

Cholecystokinin (CCK): CCK is an 8-amino acid gut peptide released in response to a caloric load. It circulates and binds to CCK_A receptors in the pylorus, vagus nerve, NTS, and area postrema *(7)* to promote satiety.

Metabolic Afferents Controlling Energy Balance

Leptin: The balance of energy intake and expenditure is normally regulated very tightly (within 0.15% per year) by the hormone leptin. Leptin is a 167-amino acid hormone produced by white adipocytes. Leptin's primary neuroendocrine role is to mediate information about the size of peripheral adipocyte energy stores to the VMH *(4,21)*. As such, it is a prerequisite signal to the VMH for the initiation of high-energy processes such as puberty and pregnancy *(22,23)*. Leptin reduces food intake and increases the activity of the sympathetic nervous system (SNS) *(24)*. Conversely, low leptin levels infer diminished energy stores, which impact on the VMH to increase food intake and reduce energy expenditure. Serum leptin concentrations drop precipitously (and to a greater degree than fat mass) during short-term fasting *(25,26)*, and it seems likely that leptin functions more as a peripheral signal to the hypothalamus of inadequate caloric intake than as a hunger or satiety signal per se *(27)*.

In the fed state, circulating levels of leptin correlate with percent body fat *(28,29)*. Leptin production by adipocytes is stimulated by insulin and glucocorticoids *(30,31)* and inhibited by β-adrenergic stimulation *(27)*. Programming of relative leptin concentrations by early caloric intake may be one mechanism that links early overnutrition with later obesity *(32)*.

Leptin binds to its receptor (a member of the Class 1 cytokine receptor superfamily) on target VMH neurons. There are four receptor isoforms formed by differential splicing: ObRa, an isoform with a shortened intracellular domain, which may function as a transporter; ObRb, the intact full-length receptor; ObRc, also with a short intracellular domain; and ObRe, which lacks an intracellular domain and functions as a soluble receptor *(33)*.

As leptin binds to its VMH receptor, three neuronal signals are transduced. The first is opening of an ATP-sensitive potassium channel, which hyperpolarizes the neuron and decreases its firing rate *(34)*. The second is the activation of a cytoplasmic Janus kinase 2 (JAK2), which phosphorylates a tyrosine moiety on proteins of a family called signal transduction and transcription (STAT-3) *(35)*. The phosphorylated STAT-3 translocates to the nucleus, where it promotes leptin-dependent gene transcription *(36)*. Third, leptin activates the insulin receptor substrate 2/phosphatidylinositol-3-kinase (IRS2/PI3K) second messenger system in ARC neurons, which increases neurotransmission of the central anorexigenic signaling pathway *(37)*.

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Fig. 2. (continued) ACh, acetylcholine; DAG, diacylglycerol; DMV, dorsal motor nucleus of the vagus; 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; LC, locus coeruleus; LHA, lateral hypothalamic area; LPL, lipoprotein lipase; MARCKS, myristoylated alanine-rich protein kinase C substrate; NE, norepinephrine; PIP_2, phosphatidylinositol pyrophosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PVN, paraventricular nucleus; $SSTR_5$, somatostatin-5 receptor; TG, triglyceride; V_{Ca}, voltage-gated calcium channel; VMH, ventromedial hypothalamus; SUR, sufonylurea receptor. From Lustig *(21)*. (Courtesy of Nature Publishing Group, with permission.)

Insulin: Insulin plays a critical role in energy balance *(38)*. In peripheral tissues it promotes glycogenesis, muscle protein synthesis, and fat storage and regulates the production and action of neuroendocrine modulators of nutrient uptake and metabolism. But insulin is also transported across the blood–brain barrier and binds to receptors in a subpopulation of VMH neurons *(39,40)*, suggesting that it acts centrally to regulate food intake. Indeed in animals, acute and chronic intracerebroventricular insulin infusions decrease feeding behavior and induce satiety *(41–43)*. The data on acute and chronic peripheral insulin infusions are less clear. Studies of overinsulinized diabetic rats demonstrate increased caloric intake (in order to prevent subacute hypoglycemia) and the development of peripheral insulin resistance *(44,45)*. Chronic peripheral insulin infusions in experimental animals decrease hepatic and skeletal muscle glucose uptake by reducing Glut4 expression but do not alter adipose tissue glucose uptake *(46,47)*. One human study injecting short-term insulin peripherally during meals did not demonstrate an effect on satiety *(48)*. Insulin acutely activates the insulin receptor substrate 2/phosphatidylinositol-3-kinase (IRS2/PI3K) second messenger system in arcuate nucleus (ARC) neurons *(49)*, which increases neurotransmission of the central anorexigenic signaling pathway (see below). The importance of CNS insulin action was underscored by the phenotype of a brain (neuron)-specific insulin receptor knockout (NIRKO) mouse, which cannot transduce a CNS insulin signal *(50)*. NIRKO mice become hyperphagic, obese, and infertile with age and have high peripheral insulin levels. These findings suggest that peripheral insulin mediates a satiety signal in the VMH to help control energy balance *(51)*. Various knockouts of the insulin signal transduction pathway that reduce insulin signaling lead to an obese phenotype *(52,53)*, while those that increase insulin signaling lead to a lean phenotype *(54,55)*.

CENTRAL PROCESSING

Peripheral afferent (neural and hormonal) signals reaching VMH neurons are integrated by a gated neural circuit designed to control both energy intake and expenditure (Fig. 2). This circuit consists of two arms: the anorexigenic arm, which contains neurons expressing the co-localized peptides proopiomelanocortin (POMC) and cocaine/amphetamine-regulated transcript (CART), and the orexigenic arm, which contains neurons with the co-localized peptides neuropeptide Y (NPY) and agouti-related protein (AgRP). Ghrelin receptor immunoreactivity co-localizes with NPY and AgRP neurons, while insulin and leptin receptors are located on both POMC/CART and NPY/AgRP neurons in the VMH *(56)*, suggesting divergent regulation of each arm. These two arms compete for occupancy of melanocortin receptors (MCRs; either MC_3R or MC_4R) in the PVN and LHA.

Anorexigenesis, POMC/α-MSH, and CART

POMC is differentially cleaved in different tissues and neurons. The ligand α-melanocyte-stimulating hormone (α-MSH) is the primary product involved in anorexigenesis. Both overfeeding and peripheral leptin infusion induce the synthesis of POMC and α-MSH within the ARC *(57)*. α-MSH induces anorexia by binding to melanocortin receptors within the PVN or LHA. CART is a hypothalamic neuropeptide induced by leptin and reduced by fasting. Intrahypothalamic infusion blocks appetite, while antagonism of endogenous CART increases caloric intake *(58)*.

Orexigenesis, NPY, and AgRP

NPY and AgRP co-localize to a different set of neurons within the ARC, immediately adjacent to those expressing POMC/CART *(59)*. NPY has numerous functions within the hypothalamus, including initiation of feeding, puberty, and regulation of gonadotropin secretion and adrenal responsiveness *(60,61)*. NPY is the primary orexigenic peptide. ICV infusion of NPY in rats causes hyperphagia,

energy storage, and obesity *(62,63)*. These actions are mediated through Y_1 and Y_5 receptors. Fasting and weight loss increase NPY expression in the ARC, accounting for increased hunger, while PYY_{3-36} (through Y_2 receptors) and leptin decrease NPY mRNA *(17,64)*.

AgRP is the human homolog of the protein agouti, which is present in abundance in the yellow $(A^y\text{-}a)$ mouse *(65)*. This protein is an endogenous competitive antagonist of all melanocortin receptors (MCR), accounting for the yellow color in these mice. In the presence of large amounts of AgRP at the synaptic cleft in the PVN, α-MSH cannot bind to the MC_4R to induce satiety *(66)*.

Other Neuroendocrine Modulators of Energy Balance

Norepinephrine (NE): NE neurons in the locus coeruleus synapse on VMH neurons to regulate food intake *(67)*. The actions of NE on food intake seem paradoxical, as intrahypothalamic NE infusions stimulate food intake through effects on central $α_2$- and β-adrenergic receptors *(68)*, whereas central infusion of $α_1$-agonists markedly reduces food intake *(69)*.

Serotonin (5-HT): Five lines of evidence impicate a role for 5-HT in the perception of satiety: (1) Injection of 5-HT into the hypothalamus increases satiety, particularly with respect to carbohydrate *(70)*; (2) central administration of $5\text{-}HT_{2c}$ receptor agonists increases satiety, while antagonists induce feeding *(71)*; (3) administration of selective 5-HT reuptake inhibitors induces early satiety *(72)*; (4) leptin increases 5-HT turnover *(73)*; and (5) the $5\text{-}HT_{2c}$R-KO mouse exhibits increased food intake and body weight *(74)*. The role of 5-HT in the transduction of the satiety signal may have both central and peripheral components, as intestinal 5-HT secreted into the bloodstream during a meal may impact GI neuronal function and muscle tone while binding to 5-HT receptors in the NTS (see earlier) to promote satiety *(75)*.

Melanin-concentrating hormone (MCH): MCH is a 17-amino acid peptide expressed in the zona incerta and LHA. MCH neurons synapse on neurons in the forebrain and the locus coeruleus. MCH appears to be important in behavioral responses to food such as anxiety and aggression *(76)*. Expression of the peptide is upregulated in *ob/ob* mice. MCH knockout mice are hypophagic and lean *(77)*, while transgenic MCH-overexpressing mice develop obesity and insulin resistance *(78)*. ICV administration of MCH stimulates food intake, similar to that seen with NPY administration *(79)*.

Orexins A and B: These 33- and 28-amino acid peptides, respectively, have been implicated in both energy balance and autonomic function in mice *(80)*. Orexin knockout mice develop narcolepsy, hypophagia, and obesity *(81)*, suggesting that orexins bridge the gap between the afferent and efferent energy balance systems *(82)*. Orexins in the LHA stimulate neuropeptide Y (NPY) release, which may account for their induction of food intake; they also increase corticotropin-releasing factor (CRF) and sympathetic nervous system (SNS) output to promote wakefulness, energy expenditure, learning and memory, and the hedonic reward system (see later) *(83)*. Conversely, orexin neurons in the perifornical and dorsomedial hypothalamus regulate arousal and the response to stress.

Endocannabinoids (ECs): It has long been known that marijuana and its major constituent tetrahydrocannabinol stimulate food intake. Recently, endogenous ECs and the CB_1 receptor have been linked to energy balance and the metabolic syndrome *(84)*. The CB_1 receptor is expressed in corticotropin-releasing factor (CRH) neurons in the PVN, in CART neurons in the VMN, and in MCH- and orexin-positive neurons in the LHA and perifornical region. Fasting and feeding are associated with high and low levels of ECs in the hypothalamus, respectively. CB_1 receptor knockout mice have increased CRH and reduced CART expression. Hypothalamic EC levels are increased in leptin-deficient *ob/ob* mice; intravenous leptin reduces EC levels, indicating that a direct negative control is exerted by leptin on the EC system. Glucocorticoids increase food intake in part by stimulating EC synthesis and secretion, while leptin blocks this effect *(85)*. Finally, the presence of CB_1 receptors on

afferent vagal neurons suggests that endocannabinoids may be involved in mediating satiety signals originating in the gut.

Melanocortin Receptors (MCR) and Central Neural Integration

The human MC_4R localizes to chromosome 2 and is a 7-transmembrane G-coupled receptor, encoded by an intronless 1 kB gene. The binding of hypothalamic α-MSH to the MC_4R in the PVN and LHA results in a state of satiety, whereas ICV administration of MC_4R antagonists stimulates feeding. These observations suggest that the MC_4R transduces satiety information on caloric sufficiency. The role of the MC_4R in human obesity is well known; in some studies, 2.5–5% of morbidly obese adults had heterozygous mutations in the MC_4R *(86)*. In the MC_3R knockout mouse, a different phenotype is seen. These animals are obese but hypophagic and have increased body fat relative to lean body mass. They gain weight on either low- or high-fat chow and do not change caloric oxidation in response to changes in dietary fat content. These findings suggest a defect in energy expenditure *(87)*. The role of the MC_3R in human obesity is less clear. Functional variants of the MC_3R have been noted in certain populations *(88,89)*. One hypothesis is that the MC_4R modulates energy intake, while the MC_3R modulates energy expenditure *(90)*.

THE EFFERENT SYSTEM

The MCRs in the PVN and LHA transduce signals emanating from the VMH in order to modulate activity of the sympathetic nervous system (SNS), which promotes energy expenditure, and the efferent vagus, which promotes energy storage (Fig. 2).

The Sympathetic Nervous System (SNS) and Energy Expenditure

Anorexigenic pressure increases energy expenditure through activation of the SNS *(91)*. For instance, leptin administration to *ob/ob* mice increases brown adipose tissue thermogenesis, renovascular activity, and spontaneous motor activity; all are associated with increased energy expenditure and facilitate weight loss *(92)*. Similarly, insulin administration acutely increases SNS activity in normal rats and in humans *(93,94)*.

The SNS increases energy expenditure by activating lipolysis in white and brown adipose tissue and promoting energy utilization in skeletal and cardiac muscle. Binding of catecholamines to muscle $β_2$-adrenergic receptors *(95)* stimulates glycogenolysis, myocardial energy expenditure, and increases in glucose and fatty acid oxidation and increases protein synthesis *(96,97)*. Binding to $β_3$-adrenergic receptors in white and brown adipose tissue increases cAMP, which activates protein kinase A (PKA) *(98)*. In white adipose PKA activates hormone-sensitive lipase, which generates ATP from hydrolysis of triglyceride. In brown fat PKA phosphorylates CREB, which induces expression of PGC-1α. PGC-1α in turn binds to the uncoupling protein-1 (UCP-1) promoter and increases its expression *(99,100)*.

UCP1 is an inner membrane mitochondrial protein that uncouples proton entry from ATP synthesis *(101)*; therefore, UCP1 expression dissipates energy as heat and thereby reduces the energy efficiency of brown fat. UCP1 is induced by FFAs derived from triglyceride breakdown; FFAs released from adipocytes are transported to the liver, where they are utilized for energy through ketogenesis. Lipolysis reduces leptin expression; thus a negative feedback loop is achieved between leptin and the SNS (Fig. 2).

The Efferent Vagus and Energy Storage

In response to declining levels of leptin and/or persistent orexigenic pressure, the LHA and PVN send efferent projections residing in the medial longitudinal fasciculus to the dorsal motor nucleus of

the vagus nerve (DMV), activating the efferent vagus *(102)*. The efferent vagus opposes the SNS by promoting energy storage in four ways: (a) it reduces myocardial oxygen consumption by reducing heart rate; (b) it increases nutrient absorption by promoting GI peristalsis and pyloric opening; (c) it increases insulin sensitivity by potentiating the uptake of glucose and FFA into adipose tissue; and (d) it increases postprandial insulin secretion, which increases fat deposition *(103–106)*.

Retrograde tracing of white adipose tissue reveals a wealth of efferents originating at the DMV *(106)*. These efferents synapse on M_1 muscarinic receptors, which increase insulin sensitivity. Denervation of white adipose tissue reduces glucose and FFA uptake and increases HSL expression. Thus, vagal modulation of the adipocyte augments storage of both glucose and FFAs by improving adipose insulin sensitivity and reducing triglyceride breakdown *(107)* (Fig. 2).

The DMV also sends efferent projections to the β-cells of the pancreas *(108)*. This pathway is responsible for the "cephalic" or preabsorptive phase of insulin secretion, which is glucose independent and can be blocked by atropine *(109)*. Overactive vagal neurotransmission increases insulin secretion from β-cells in response to an oral glucose load through three distinct but overlapping mechanisms (Fig. 2; see the Chapter 26 on Hypothalamic Obesity for full discussion): (1) the muscarinic activation of a sodium channel, resulting in increased β-cell depolarization; (2) the muscarinic activation of β-cell phospholipases which hydrolyze intracellular phosphatidylinositol to diacylglycerol (DAG) and inositol triphosphate (IP_3), inducing insulin vesicular exocytosis; and (3) the stimulation of GLP-1 from intestinal L-cells, which activates protein kinase A and increases insulin exocytosis. Vagal induction of insulin secretion promotes lipogenesis through increased expression of Glut 4, acetyl-CoA carboxylase, fatty acid synthase, and lipoprotein lipase *(110,111)*.

THE HEDONIC PATHWAY OF FOOD REWARD

Hypothalamic feedback systems are modulated by a "hedonic pathway" that mediates the pleasurable and motivational responses to food. The hedonic pathway comprises 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. Food intake is a readout of the hedonic pathway; administration of morphine to the NA increases food intake in a dose-dependent fashion *(112)*. Functional suppression of the hedonic pathway curtails food intake when energy stores are replete; dysfunction or continuous activation of the hedonic pathway can increase food intake and promote excessive weight gain.

The VTA appears to mediate feeding on the basis of palatability rather than energy need. The dopaminergic projection from the VTA to the NA mediates the motivating, rewarding, and reinforcing properties of various stimuli, such as food and addictive drugs. 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 *(113)*. For instance, fasting and food restriction (when insulin and leptin levels are low) increase the addictive properties of drugs of abuse, while central leptin administration can reverse these effects *(114)*. Food deprivation in rodents increases addictive behavior and the pleasurable responses to a food reward, as measured by dopamine release and dopamine receptor signaling *(115)*. Conversely, 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 *(116)*. Furthermore, insulin appears to inhibit the ability of VTA agonists (e.g., opioids) to increase intake of sucrose *(117)*. Finally, insulin blocks the ability of rats to form a conditioned place preference association to a palatable food *(118)*.

The role of the hedonic pathway in human obesity is not yet elucidated, but can be surmised. Dopamine D_2 receptor abundance is inversely related to BMI; the depression of dopaminergic activity

in obese subjects might trigger a "reward-seeking" increase in food intake that promotes further weight gain. This may explain in part the higher risk of obesity in patients taking drugs that block D_2 receptors (e.g., antipsychotics *(119)*). Alternatively, the down-regulation of dopaminergic activity in obese subjects may be an adaptive response to prior weight gain. Under normal circumstances, leptin and insulin signal adipose and nutrient sufficiency to the VTA, suppressing dopamine neurotransmission and the reward of food *(113)*. However, these negative feedback loops are blocked in states of insulin and leptin resistance that characterize obesity *(120)*.

Positron emission tomography suggests that hunger and satiety neuronal circuits in the VMH connect with other regions of the limbic system *(121)* that control primal emotions, reproductive activity, and survival instinct; a primal "reward" or pleasure response might explain ingestive behavior in the absence of hunger, a common finding in obese children and adults. It has been argued that much of the impasse in efforts to both treat and prevent obesity stems from the intrinsic difficulty of overriding instinct with reason *(122)*.

THE AMYGDALA AND THE STRESS PATHWAY OF FOOD INTAKE

The VMH and VTA-NA mediate satiety when energy stores are replete, but appear to be overridden by amygdala activation and the concomitant stress response associated with insulin resistance *(123)*. Stress hormones such as the glucocorticoids are essential for the full expression of obesity in rodents and humans and may explain the disruptive role that stress plays in weight regulation *(124)*.

Stress and glucocorticoids are integral in promoting the constellation of features characteristic of the metabolic syndrome. Studies of adrenalectomized (ADX) rats supplemented with corticosterone demonstrate that exogenous fat intake is directly proportional to circulating corticosterone concentrations *(125,126)*. In intact rats, corticosterone stimulates intake of high-fat food; likewise, cortisol administration increases food intake in humans *(127)*. Human research shows increased caloric intake of "comfort foods" (i.e., those with high energy density) after acute stress *(128)*. Moreover, several studies in children have observed relationships between stress and unhealthy dietary practices, including increased snacking and an elevated risk of weight gain during adolescence and adulthood *(129,130)*.

NPY and catecholamines co-localize in sympathetic neurons in the peripheral nervous system as well as the central nervous system. In response to chronic stress, peripheral neurons express more NPY, which stimulates endothelial cell (angiogenesis) and preadipocyte proliferation, differentiation, and adipogenesis by activating Y2 receptors in visceral adipose tissue. This causes abdominal obesity, inflammation, hyperlipidemia, hyperinsulinemia, glucose intolerance, hepatic steatosis, and hypertension, reproducing the features of the human metabolic syndrome. Conversely, local intra-fat Y2R antagonists or adenoviral Y2R knock-down reverses or prevents fat accumulation and metabolic complications *(131)*. This suggests that acute stress causes lipolysis and weight loss, but chronic stress "hijacks" the SNS, increasing NPY expression to cause visceral fat accumulation and metabolic dysfunction.

NEGATIVE FEEDBACK OF ENERGY BALANCE – THE RESPONSE TO CALORIC DEPRIVATION

The response to caloric deprivation serves as a model for understanding the regulation of energy balance and the adaptation to weight loss. Everyone appears to have a "personal leptin threshold," probably genetically determined, above which the brain interprets a state of energy sufficiency *(132)*. The leptin-replete fed state is characterized by increased physical activity, decreased appetite, and feelings of well-being. In response to caloric restriction, leptin levels decline even before weight

loss is manifest *(25,26)*. This is interpreted by the VMH as starvation. Gastric secretion of ghrelin increases; this stimulates pituitary GH release, which promotes lipolysis to provide energy substrate for catabolism. Ghrelin also stimulates the expression of NPY/AgRP, which antagonizes α-MSH/CART and reduces MC_4R occupancy. The resultant lack of anorexigenic pressure on the MC_4R increases feeding behavior, reduces fat oxidation, and promotes fat deposition. Fat storage is facilitated by increases in insulin sensitivity.

Total and resting energy expenditure decline in an attempt to conserve energy *(133)*; the fall in leptin reduces plasma T3 levels, and UCP1 levels in adipose tissue decline *(134)* as a result of decreased SNS activity *(135)*. Yet, in spite of decreased SNS tone at the adipocyte, there is an obligate lipolysis due to insulin suppression and upregulation of hormone-sensitive lipase. Lipolysis is necessary to maintain energy delivery to the musculature and brain in the form of liver-derived ketone bodies.

Under conditions of fasting or caloric deprivation, vagal tone is increased. Together with the fall in T3 levels, this slows the heart rate and reduces myocardial oxygen consumption. Heightened vagal tone also increases β-cell insulin secretion and adipose insulin sensitivity; in sum, these effects promote increased energy fat storage *(135)*. The effects of fasting revert once caloric sufficiency is re-established and leptin levels rise.

Thus the adaptive/compensatory response to fasting or caloric deprivation is designed to re-establish homeostasis and recover lost weight by inducing food intake and reducing energy expenditure; this explains the great difficulty that most obese people have in achieving or maintaining long-term weight loss.

LEPTIN RESISTANCE

Most obese children have high leptin levels but do not have receptor mutations, manifesting what is commonly referred to as "leptin resistance." Leptin resistance prevents exogenous leptin administration from promoting weight loss *(136)*. The response to most weight loss regimens plateaus rapidly due to the rapid fall of peripheral leptin levels below a personal "leptin threshold" *(137)*, which is likely genetically determined. Leptin decline causes the VMH to sense a reduction in peripheral energy stores. This fosters a decrease in REE to conserve energy, analogous to the starvation response described earlier *(133)* but occurring at elevated leptin levels.

The cause of leptin resistance in obesity is likely multifactorial. First, leptin crosses the blood–brain barrier via a saturable transporter, which limits the amount of leptin reaching its receptor in the VMH *(138,139)*. Second, activation of the leptin receptor induces intraneuronal expression of suppressor of cytokine signaling-3 (SOCS-3), which limits leptin signal transduction *(54)*. Finally, hypertriglyceridemia limits access of peripheral leptin to the VMH *(140)* and interferes with leptin signal transduction upstream of STAT-3, its primary second messenger *(141)*. Thus, factors that induce hypertriglyceridemia, such as dietary fructose and insulin resistance, tend to promote leptin resistance *(21)*.

Two clinical paradigms have been shown to improve leptin sensitivity. After weight loss through caloric restriction, exogenous administration of leptin can then increase REE back to baseline and permit further weight loss *(142,143)*. This suggests that weight loss itself improves leptin sensitivity. Second, suppression of insulin correlates with improvement in leptin sensitivity and promotes weight loss *(144)*, suggesting that hyperinsulinemia promotes leptin resistance by interfering with leptin signal transduction in the VMH and VTA *(145)*. Indeed, insulin reduction strategies may be effective in promoting weight loss in obese children by improving leptin sensitivity *(146)*. This has led to the hypothesis that chronic hyperinsulinemia functions to block leptin signal transduction at the VMH and VTA, which turns a negative feedback cycle into a vicious feedforward cycle (Fig. 3) *(147)*. However, this hypothesis remains to be proven.
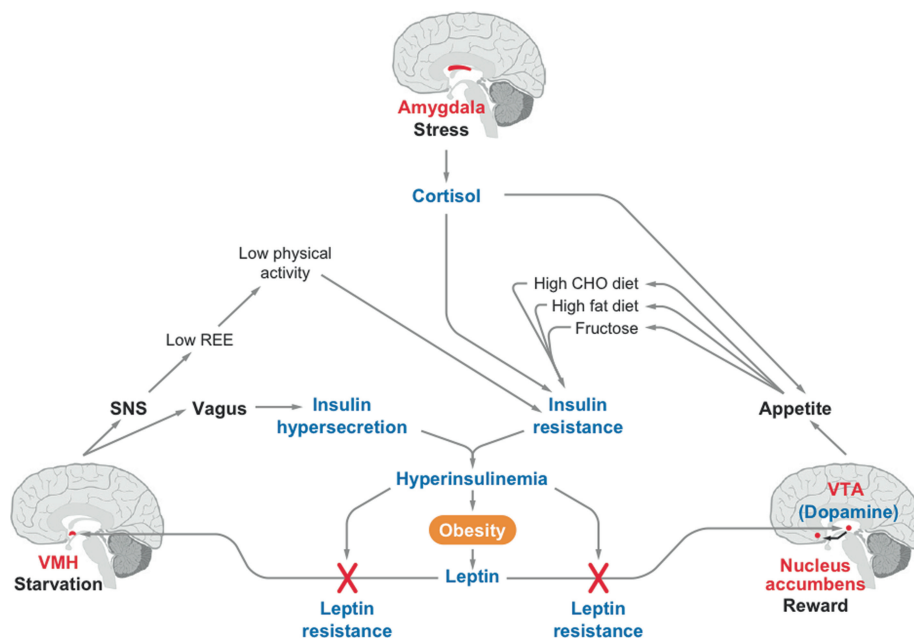
Fig. 3. The "limbic triangle." Three areas of the CNS conspire to drive food intake and reduce physical activity, resulting in persistent weight gain. The ventromedial hypothalamus (VMH) transduces the leptin signal from adipocytes to reduce energy intake and increase energy expenditure; however, hyperinsulinemia inhibits leptin signaling, promoting the "starvation response." The ventral tegmental area (VTA) transduces the leptin signal to reduce dopamine neurotransmission to the nucleus accumbens (NA) to reduce palatable food intake; however, insulin resistance and leptin resistance increase dopamine neurotransmission and promote the "reward" of food. The amygdala transduces fear and stress, resulting in increased cortisol, which also drives energy-rich food intake and promotes insulin resistance, further interfering with leptin signaling at the other two CNS sites. Thus, interference with any of the negative feedback aspects of the "limbic triangle" transforms it into a positive feedback loop, promoting continued weight gain and obesity. From Mietus-Snyder and Lustig *(147)*. (Courtesy of Annual Reviews, with permission.)

SUMMARY

It is clear that childhood obesity is not just the outcome of "gluttony" and "sloth." Rather, genetic and environmental factors alter the neurohormonal milieu, driving the propensity for both increased energy storage and decreased energy expenditure. When this feedback pathway is perturbed, it becomes a feedforward pathway, with resultant weight gain and worsening leptin resistance. The biochemistry of energy balance and the psychology and sociology of food intake have thereby converged to create an obesity epidemic with serious personal and public health ramifications.

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