ANALYTIC REVIEW

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Appetite Regulation: Hormones, Peptides, and Neurotransmitters and Their Role in Obesity

Abstract: *Understanding body weight regulation will aid in the development of new strategies to combat obesity. This review examines energy homeostasis and food intake behaviors, specifically with regards to hormones, peptides, and neurotransmitters in the periphery and central nervous system, and their potential role in obesity. Dysfunction in feeding signals by the brain is a factor in obesity. The hypothalamic (arcuate nucleus) and brainstem (nucleus tractus solitaris) areas integrate behavioral, endocrine, and autonomic responses via afferent and efferent pathways from and to the brainstem and peripheral organs. Neurons present in the arcuate nucleus express pro-opiomelanocortin, Neuropeptide Y, and Agouti Related Peptide, with the former involved in lowering food intake, and the latter two acutely increasing feeding behaviors. Action of peripheral hormones from the gut, pancreas, adipose, and liver are also involved in energy homeostasis. Vagal afferent neurons are also important in regulating energy homeostasis. Peripheral signals respond to the level of stored and currently available fuel. By studying their actions, new agents maybe developed that disable orexigenic responses and enhance anorexigenic signals. Although there are relatively few medications currently available for obesity treatment, a number of agents are in development that work through these pathways.*

Keywords: food intake; energy homeostasis; appetite; gut hormones; lipostatic hypothesis

Obesity is a growing epidemic not just in the United States but also worldwide. Globally, more than 2 billion adults and children are classified based on body mass index (BMI) as overweight (BMI 25.0 to 29.9 kg/m^2) or obese (BMI ≥ 30.0 kg/m^2).[1] In the United States, more than two thirds have a BMI greater than 25.0 kg/m^2 and nearly one half are obese.[2] These alarming statistics are apparent across nearly all demographic groups. Furthermore, it is predicted that by 2020 nearly 75% of adults in the United States will be overweight or obese.[3] In its simplest form, obesity is an imbalance between energy expenditure and energy intake with a relative greater prolonged energy intake than energy expenditure leading to excessive energy storage. The

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health ramifications of obesity include, but are not limited to, type 2 diabetes, cardiovascular disease, certain types of cancer, osteoarthritis, mobility limitations, poor mental health, and all-cause mortality.[4,5] Unfortunately, current treatments, with the exception of bariatric surgeries, are mostly ineffective.[6] Because bariatric surgeries are mostly irreversible with possible long-term complications, and large

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costs, their use for the masses are implausible. Therefore, new strategies need to be developed. This review examines energy homeostasis and food intake behaviors, specifically with regards to hormones, peptides, and neurotransmitters in the periphery and central nervous system (CNS), and their potential role in obesity. Afferent and efferent signals regulate both components of energy balance—energy intake and energy expenditure.

However, further understanding of body weight control, specifically with regard to feeding behaviors, is needed. A number of regulatory processes are discussed in this article, including the lipostatic theory, which is based on the release of leptin from adipocytes and its signaling cascade in the brain. This is an example of the peripheral signals integrating with the brain to regulate food intake and energy expenditure. Altering a body's net energy balance leads to opposing changes in energy expenditure and/or food intake to minimize body weight changes.[7] The "set-point" hypothesis was derived from these observations, which suggests that physiological systems alter food intake and energy expenditure to regulate body weight. Alternatively, the "settling-point" states that external environmental factors (ie, diet and lifestyle) determine body weight regulation. There is continuing debate among these 2 theories.[8] Whereas the physiological factors of hormones and neural innervation are the basis for this article, the mention of the nonregulatory approach is added for context. Based on the epidemic outbreak of obesity, body weight regulation is not strictly regulated. Manipulating the environment such as with portion size, energy density of the food, or the social situation leads to changes in food intake. However, total compensation for these manipulations do not occur, at least acutely.[9] For example, omitting breakfast does not lead to overconsumption of subsequent meals and snacks during the day as total daily intake is reduced when breakfast is skipped.[9] Therefore, according to the "settling-point" hypothesis, altering the environment may be the key to treating and/or preventing obesity.

Role of the Brain

Body weight regulation is based on the ability of the brain, particularly the hypothalamus, to integrate behavioral, endocrine, and autonomic responses via afferent and efferent pathways from and to the brainstem and peripheral organs.[10,11] In addition to the CNS, a number of peripheral organs and organ systems are involved in energy balance, including the liver, pancreas, adipose, gut, and muscle. A diverse range of neural and hormonal messages from these organs regarding the body's energy status—both stored and recently ingested—are presented to the brain and the brain interprets this information.[12] Energy consumption, energy expenditure, and metabolism of nutrients are thus influenced by these signals. Ultimately, this control is required by the body to ensure adequacy of nutrient availability for current needs and for stored energy during times when energy intake is limited.[13] Dysfunction in generating signals or in the interpretation of these signals by the brain is a factor in obesity as well as undernourishment from eating disorders.

Work from the 1950s demonstrated the importance of the action of the brain in energy homeostasis. Depending on the location, specific lesions of nuclei in the hypothalamus caused either profound increases or decreases in food intake and body weight.[14,15] In addition to the hypothalamus, the brainstem, which includes the nucleus tractus solitaris, area postrema, and dorsal vagal nucleus, has a critical role in body weight regulation. Specifically, the nucleus tractus solitaris behaves as a relay center and passes on the signals received from the periphery, in the form of neural inputs or circulating factors, to the hypothalamus. The area postrema, lying near the nucleus tractus solitaris, detects circulating hormones and nutrients and then provides this information to the hypothalamus by both efferent and afferent projections, thus allowing it to moderate food intake based on nutritional needs.[16,17] The amygdala in the limbic system, which is the integrative center for emotions and emotional behavior, has high levels of neurotransmitters with anorexigenic and orexigenic actions.[18-20]

The area of the hypothalamus that appears to be most critical in the integration of signals regarding energy flux is the arcuate nucleus. It receives proximal satiation signals, which interact with adiposity derived signals. The arcuate nucleus contains melanocortin system neurons that express pro-opiomelanocortin (POMC), which is a precursor for a number of peptides, including α-melanocyte stimulating hormone (α-MSH), endorphins, and adrenocorticotropic hormone, among others.[21-24] The primary receptor for α-MSH is melanocortin 4 receptor (MC4R), and it is present in the arcuate nucleus as well as several other brain areas.[25-28] Binding of either α-MSH or an agonist to MC4R activates catabolic pathways and leads to hypophagia, thermogenesis, and weight loss,[29-33] whereas MC4R antagonists elicit hyperphagia and weight gain.[34] Mice devoid of MC4R are obese with hyperphagia, and excessive fat mass.[35-37] Furthermore, a mutation in human MC4R is the most common monogenic form of human obesity, present in 1% to 2.5% of humans with a BMI above 30.0 kg/m^2.[31,38,39]

Lying adjacent to the POMC catabolic neuron, the arcuate nucleus also houses anabolic neurons. These neurons synthesize Neuropeptide Y (NPY) and Agouti Related Peptide (AgRP).[21-23,40] NPY binds to Y receptors to acutely increase food intake, leading to subsequent weight gain.[41,42] Consistent with this action, NPY secretion in the hypothalamus increases during fasting.[43] Additionally, hypothalamic administration of NPY increases food intake.[44] AgRP, a reverse agonist to MC4R receptors, competes with α-MSH for binding to the receptor, leading to increases in food intake and weight gain.[11,42,45-49] AgRP is expressed only in neurons in the arcuate nucleus that also produce NPY.[48,50]

Other hypothalamic areas involved in feeding behaviors that communicate with the arcuate nucleus are the paraventricular nucleus, the dorsomedial nucleus, and the lateral nucleus. The paraventricular nucleus is activated by neurons from the arcuate nucleus and express peptides that are primarily catabolic (nesfatin, oxytocin, thyroid releasing hormone, corticotropin releasing hormone).[51,52] On the other hand, the dorsomedial nucleus receives inputs from the anabolic NPY and AgRP neurons that originate in the arcuate nucleus.[18,53] Neurons with melanin concentrating hormone are present in the lateral nucleus of the hypothalamus. They express MC4R and integrate POMC, NPY, and AgRP neurons.[54-56] POMC neurons that project to the spinal cord are also involved in energy homeostasis by stimulating adaptive thermogenesis in brown adipose tissue through the MC4R sympathetic preganglionic neurons.[49]

A number of centrally acting neurotransmitters are involved in energy homeostasis through regulating food intake and/or energy expenditure. Gamma amino benzoic acid (GABA) is a neurotransmitter produced by the action of NPY and AgRP, and GABA regulates energy balance in the parabrachial nucleus, actions residing outside the hypothalamus.[57,58] Its role in obesity is evident in that removing the vesicular transporter for GABA in AgRP neurons leads to resistance to obesity induced by a high-fat diet, independent of alterations in the consumption of food.[57] Another neurotransmitter involved in regulating food intake and energy expenditure is serotonin, which is present in selected arcuate POMC neurons.[59-61] These POMC serotonin receptors are involved in regulating energy homeostasis through changes in feeding behavior, independent of energy expenditure.[61,62] Oxytocin is a centrally acting neurotransmitter and hormone with a growing interest as an antiobesity target based on its involvement in energy homeostasis.[63-66] Mice with deficiency in either oxytocin or oxytocin receptors display an obesity phenotype.[67,68] Long-term administration of oxytocin either peripherally or centrally leads to inhibition of food intake, increased energy expenditure, and weight loss in diet-induced obesity and genetically obese rodent models.[63-66,69-72] Interestingly, this effect on energy balance with oxytocin is not solely confined to rodent models as chronic administration of oxytocin to diet-induced obese rhesus monkeys reduced body weight, lowered food intake, and increased energy expenditure.[73] The primary site of oxytocin production in the brain is neurons located in parvocellular paraventricular nucleus, with less produced in the anterior hypothalamus and medial amygdala.[74] Projections from these locations go to the brainstem, including the nucleus solitaris tract and spinal cord.[75,76] Although its mechanism is not totally understood, oxytocin appears to be a downstream effector of anorexigenic signals in the arcuate nucleus and brainstem.[51,64,74,77]

Whereas the blood brain barrier serves as a protective structure for the brain to prevent damage from unwanted molecules, this brain structure is permeable to peripheral metabolic signals and allows their communication with areas of the brain that regulate energy homeostasis. The arcuate nucleus is adjacent to the median eminence, which has an incomplete blood-brain barrier with fenestrated capillaries.[78] The lack of the traditional blood-brain barrier in this hypothalamic area increases the permeability of molecules from the blood to the brain.[79-81] Furthermore, circulating factors may influence areas in the brainstem such as the nucleus tractus solitaries since the area postrema is a circumventricular organ that is adjacent to the nucleus tractus solitaries. Hormones and nutrients thus may bypass the blood-brain barrier and gain access to the 2 key areas handling energy homeostasis—the brainstem and hypothalamus.

Peripheral Signals

A number of signals originate in the peripheral organs and are in response to level of stored and currently available fuel in selected tissues.[12] These signals include both neural and hormonal messages. For the latter type, leptin and insulin reflect energy stores and have been extensively investigated. Gut peptides provide further information on current food consumption and they modify electrical activity of the vagal afferent sensory pathway by attaching to receptors on these neurons that extend into the digestive tract mucosa. These intestinal derived signals are sent via the vagus to the nucleus tractus solitaris of the brainstem, with further projection of the message to hypothalamic regions.[82]

Leptin

Hormone signals from adipose tissue were first proposed in the lipostatic hypothesis as early as the mid-1950s.[83] Kennedy observed that rats alter food intake as a homeostatic adjustment to keep body fat stores stable. For example, food intake increased with a rise in energy expenditure, which maintained constant body fat stores. Thus, Kennedy hypothesized that a circulating metabolite exerts its action on the hypothalamic region; this was supported as damage to the hypothalamus allowed the animal to overeat and to subsequently become obese.[83] This homeostatic theory of hunger allows the brain to monitor energy storage in the body. The proposed circulating metabolic factor was subsequently identified over 40 years later in 1994 as leptin.[84] Leptin is produced primarily by white adipose tissue and released into the general circulation. Plasma levels of leptin are positively correlated with total body fat as higher levels of plasma leptin are seen in those with higher body fat. However, leptin's secretion is tightly coupled to energy status as leptin levels decrease by nearly two thirds after 1 week of energy restriction.[85] Thus, plasma leptin concentrations decrease faster than the rate of reduction of adipose tissue. Furthermore, leptin is more highly correlated with subcutaneous than visceral adiposity.[86,87] Soluble leptin receptor is the main binding protein for leptin in blood and it can affect the

bioavailability and effects of leptin.[88,89] High levels of the soluble receptor reduces biologically active leptin and inhibits leptin signaling.[90] Low levels of soluble receptor also indicate low leptin activity as this may reflect low expression of the membrane bound leptin receptor, indicating leptin resistance.[91]

Early studies in obese animal models demonstrated that leptin decreases food consumption and increases energy expenditure. Animals with leptin deficiency show increased food intake, lower energy expenditure, and develop severe obesity.[92-94] Leptin exerts its action through binding to the membrane bound leptin receptor, triggering the Janus Activated Kinases (JAK) and the transcription factor signal transducer and activators of transcription (STAT) signaling cascades, among others.[30,95-97] Leptin communicates directly with the brain and acts predominately in the hypothalamus in the areas of the arcuate nucleus, ventromedial hypothalamus, and lateral hypothalamic by passing through the sparse blood-brain barrier near the hypothalamus via a saturable transporter.[21,98,99] Leptin receptors are expressed on both POMC and NPY/AgRP neurons and are highest for these neurons in the arcuate nucleus.[98] As discussed above, neuropeptides from these neurons regulate energy homeostasis.[100-104] In the arcuate nucleus, leptin stimulates gene expression and the firing rate of POMC neurons[30,105-107] and inhibits activity of NPY and AgRP neurons.[84,98,108,109] The activation of POMC neurons leads to increased production of α-MSH and binding with its receptor, MC4R, to reduce feeding behaviors.[110-112] Consistent with this mechanism, use of MC4R antagonists abolishes the effects of leptin.[113,114] Furthermore, selective deletion of leptin receptors in the CNS also eliminates the effect of leptin.

Administering leptin to rodents and humans with congenital leptin deficiency resolved obesity through decreasing food intake.[92,115-119] The implication of leptin for treating human obesity is questioned, however, as only a small fraction of humans are leptin deficient; most humans are refractory to leptin, that is, leptin resistant. This term refers to states of obesity that demonstrate hyperleptinemia as well as a lowered response to leptin. In diet-induced obese mice and in the vast majority of humans, providing leptin is inefficient in treating obesity.[119] Further supporting the concept of leptin resistance in humans are data showing that individuals that are more likely to regain weight after weight loss have higher leptin levels, consistent with lower leptin sensitivity, than those with successful weight maintenance.[120] Importantly, the causes of leptin resistance have been an active area of research with several mechanisms identified, including a dysfunction in transporting leptin into the CNS,[99,121-124] a defect in leptin signaling,[125,126] endoplasmic reticulum stress,[127-129] and alterations in the operation of the leptin receptor.[130,131] One well-studied leptin signaling pathway has been Suppressor of Cytokine Signaling (SOCS3). Interestingly, leptin signaling is attenuated by SOCS3.[132] In a negative feedback mechanism, leptin increases SOCS3 expression.[132,133] By studying this and other signaling pathways, possible therapeutic treatments may be developed for combatting leptin resistance and the obesity phenotype observed with leptin resistance.

We and others have demonstrated alterations in plasma leptin with behavioral and surgical weight loss interventions. In post Roux-en-Y gastric bypass surgery patients, leptin decreased serially up to the 6-month follow-up time point.[134] Circulating values dropped by 70% from baseline with a 30% decrease in body weight 6 months postsurgery.[134] In this morbidly obese cohort, leptin was correlated with body mass index at baseline (r = .78) and remained significantly correlated at 6 months (r = .79). Behavioral obesity treatment encompassing dietary energy restriction and exercise training also reduced leptin levels in older adults for up to 18 months, even with moderate weight loss of 5% to 10%.[135] Interestingly, change in body weight was statistically related to change in leptin over 18 months of weight loss intervention in older adults.[135]

Insulin

In addition to the well-known peripheral actions of insulin in maintaining glucose homeostasis, insulin signaling in the brain is also important for energy balance.[30,136-138] Similar to leptin, pancreatic beta cell insulin secretion occurs in response to changes in energy flux,[139] and insulin levels are proportional to body fat, for both fasting and 24-hour insulin levels.[140,141] With actions that mimic leptin, insulin decreases food intake and lower insulin levels increase food intake.[22,142-144] Insulin is critical for the integration of several peripheral metabolic signals. This is accomplished through insulin's action to inhibit NPY and stimulate POMC neurons. Insulin receptors in the blood-brain barrier facilitates its presence in the CNS. The hypothalamus, particularly the arcuate nucleus, which is rich in insulin receptors, is the gateway for insulin's access to the CNS.[145] Acute infusion of insulin into the CNS reduces food intake and body weight through binding of insulin to specific receptors on neurons in the hypothalamus, hindbrain, and other locations.[137,146,147] In contrast, chronic administration has little effect on obesity due to the development of insulin resistance.[13] Administration of insulin receptor agonists into the CNS also reduces food intake and body weight in rodents on a high-fat diet.[148] Supporting this role for insulin in feeding behaviors and subsequent body weight maintenance, mice lacking insulin receptors in the CNS are insulin resistant with increased food intake and development of diet-induced obesity.[149] In contrast to leptin, circulating levels of insulin are more highly correlated with visceral than subcutaneous fat.[13,150-152]

In addition to the lipostatic hypothesis that illustrates hormonal signals originating from white adipose tissue, this high-energy storage depot also has afferent sensory input that is received by spinal neurons and project to the brainstem, hypothalamus, and paraventricular nucleus. All of these

central areas are important in sympathetic nervous system outflow.[153] The importance of this sensory signal in energy homeostasis was apparent when denervation of sensory neurons from white adipose tissue led to increased fat pad weight.[154] Furthermore, the electrical outflow in the sensory neuron of white adipose tissue is increased with leptin injection into this tissue,[152] suggesting that this hormone may be responsible for the afferent signaling discharge. However, others demonstrated that increased adipose afferent reflex was still apparent in leptin resistance.[155,156] Furthermore, the leptin injection raised CNS sympathetic outflow to other white adipose tissue, brown adipose tissue, adrenal medulla, and liver.[157,158]

Gut Hormones

Over the past several decades, the importance of signals originating from the intestines has become apparent for energy homeostasis. Enteroendocrine cells sense nutrient content in the intestinal lumen and regulate the release of gut derived hormones. After diffusion into the hepatic portal vein, these hormones spread into the systemic circulation and alter neuronal signaling in the brain to modulate feeding.[159] The blood-brain barrier in the brainstem allows gut hormones to access the area postrema, which then communicates with the nucleus tractus solitaris. Additionally, gut hormones signal the brain by directly stimulating vagal afferent neurons.[160-163] This section will review a number of these gut hormones and their action with energy homeostasis.

CCK

Cholecystokinin (CCK) is released into the circulation from the endocrine I cells in the duodenum and jejunum in response to saturated fatty acids, long-chain fatty acids, amino acids, and small peptides.[164,165] The hormone increases the release of pancreatic enzymes and bile salts into the duodenum that promotes the digestion of fats and proteins.[166,167] The level of CCK secretion is proportional to the lipid and protein content in the meal. Actions for CCK related to the digestion and absorption of nutrients includes slowing down gastric emptying and stimulating gallbladder secretion. In its role of appetite regulation, CCK inhibits food intake and decreases meal size.[168-173] Low circulating levels of CCK are related to increased hunger and decreased fullness.[174] However, animals without CCK have normal food intake and body weight, suggesting that this signaling molecule is not essential for normal regulation of energy status.[13] CCK binds to vagal neurons that activate the hindbrain, which is responsible for integrating satiation and adiposity signals with nutrient levels, hedonic signals, and social factors[175] and relaying the information to other areas of the brain, including the hypothalamus and the reward center.[13] Support for CCK's action through the vagal afferent nerve is from work showing that lesions to the vagus nerve eliminates the CCK-induced reduction in food intake.[173] Interestingly, manipulating CCK satiation signals with pharmacological agents influences eating through affecting meal size but not the initiation of a meal.[176,177] Furthermore, early work with CCK showed that intraperitoneal administration of CCK in rats reduced meal size, but increased the number of meals such that there was no difference in total daily food intake or growth rate in rats after 6 days of treatment.[178] Leptin's involvement in CCK signaling is apparent as leptin enhances the vagal sensitivity to CCK.[179]

Ghrelin

Working through the vagal afferent pathway and the nucleus tractus solitaris, ghrelin—the hunger hormone—activates NPY and AgRP neurons and suppresses POMC neurons in the arcuate to stimulate appetite.[180-185] Inhibiting gastric vagal afferent signals[182] and blocking the NPY neuron activation mitigates ghrelin-induced feeding.[186-188] The receptor for ghrelin, growth hormone secretagogue receptor, is found centrally in similar locations to the leptin receptor.[183,184,189] The interaction between leptin and ghrelin is also seen as ghrelin reverses the inhibition of NPY and AgRP neurons by leptin and leptin antagonizes the increased food intake by ghrelin.[187] Its action requires GABA, as this neurotransmitter is released from the NPY and AgRP neurons with the binding of ghrelin to its receptor.[190] As information is received from ghrelin by the vagal afferent pathway, the orexigenic signal is transmitted to norepinephrine neurons of the nucleus tractus solitaris. This promotes norepinephrine secretion from the hypothalamus.[182]

Administration of ghrelin centrally and peripherally stimulates appetite, food intake, and weight gain.[191-194] Mice who are selectively deficient in the ghrelin receptor are hypophagic and lean when fed a high-fat diet.[195] In mice with an isolated defect in GABA transport, the orexigenic effect of ghrelin was dampened as these mice have a normal weight phenotype on a high-fat diet.[196] The orexigenic signal is then dispersed to other parts of the hypothalamus and nonhypothalamic regions by axons of POMC and NPY and AgRP neurons reaching to the dorsomedial nucleus, lateral nucleus, paraventricular nucleus, and the ventromedial nucleus. Ghrelin also modifies appetite through binding on visceral vagal afferent neurons. Both leptin and insulin dampen ghrelin-induced activation of NPY neurons.[197] Ghrelin's action in the periphery, specifically the intestine, includes increases in motility and gastric emptying.[198,199] As expected for the hunger hormone, ghrelin peaks in fasted state and before a meal and is lower following a meal, suggesting it is acting more as a meal initiator and not controlling meal size.[200] Levels of ghrelin are lower in obese than normal weight individuals,[194] and those with higher body fat, insulin, and leptin have lower ghrelin.[194,201] Circulating levels of ghrelin are higher following weight loss.[201-203]

PYY

Pancreatic Tyrosine Tyrosine (PYY_{3-36}) is a posttranslational modified truncated form of PYY_{1-36} that interacts with

specific Y receptors on vagal afferent neurons.[204] This gut peptide induces satiety and is involved in energy expenditure.[30,205-207] PYY_{3-36} also reduces gastric emptying, intestinal motility, pancreatic secretions, and absorption of fluids and electrolytes from the ileum.[208-210] Circulating levels of PYY_{3-36} are lowest during fasting, increase to a peak within 1 to 2 hours postprandial, and remain elevated for 6 hours.[211] PYY_{3-36} activates POMC neurons and suppresses NPY in the arcuate nucleus.[207] Actions of PYY_{3-36} also occur through vagal stimulation in the brainstem.[212] Peripheral administration of PYY_{3-36} decreases food intake.[207,211,213-215] Consistent with this action, obese have lower circulating levels than lean individuals.[207,211] Interestingly, resistance to PYY is not thought to be present in obesity.

GLP-1

An incretin produced by the L cells of the intestine, glucagon like peptide 1 (GLP-1) is formed from the posttranslational modification of the proglucagon peptide. The increased glucose-stimulated insulin release occurs following binding of GLP-1 to specific receptors on pancreatic beta cells in response to glucose.[216,217] Increased initial GLP-1 release occurs in response to neural reflex or circulating factors.[218,219] A subsequent second phase of release ensues from the presence of food in the distal gut.[220,221] The levels peak by 90 minutes and the rise in plasma GLP-1 is proportional to calories consumed.[160,222] In addition to enhancing glucose stimulated insulin secretion with insulinotropic and glucagonostatic actions,[223] GLP-1 slows gastric emptying and inhibits gastric acid secretion.[224,225] By slowing gastric emptying, the need for insulin is lowered as the rate of glucose appearance in the blood is reduced.[226] The ileal brake resulting from the appearance of undigested carbohydrates, lipids, and protein in the ileum leads to GLP-1 and PYY release. This braking slows intestinal motility to allow more efficient digestion and nutrient absorption. Central neurons with GLP-1 receptors are found in the brainstem, including the nucleus of the solitary tractus and ventrolateral medulla.[227] There are projections to hunger centers in the lateral hypothalamus and periventricular areas.[228] The paraventricular hypothalamus and arcuate nucleus are also rich in GLP-1 receptors.[162,163] GLP-1 reduces food intake, increases satiety, and promotes weight loss through its peripheral and central actions.[229-232] Acute intracerebroventricular administration of GLP-1 inhibits food intake, and antagonists to the GLP-1 receptor increases food intake, even in satiated rats.[230,233] Direct administration of GLP-1 into the paraventricular nucleus has a strong inhibition of food intake, suggesting it is the primary site for brain-derived GLP-1 satiation[234,235]; however GLP-1 also produces anorexic effects in the arcuate nucleus as POMC neurons express GLP-1 receptors.[235] Furthermore, GLP-1 is lower in obese than lean individuals.[236] As satiation signals like CCK and GLP-1 are produced during food consumption neural circuits are activated and food intake decreases, ending the meal. Long-term central and subcutaneous injections of GLP-1 reduces weight gain and leads to weight loss.[237]

Oxyntomodulin

The gut peptide oxyntomodulin is also secreted from intestinal L cells in response to food ingestion and it is a product of preproglucagon. Oxyntomodulin delays gastric emptying and lowers gastric acid secretion.[238] It is known to lower food intake[239] and chronic preprandial peripheral administration of oxyntomodulin increased weight loss in humans.[240] Part of the weight loss may be attributed to increased energy expenditure as oxyntomodulin increased activity related energy expenditure in pair-fed rats.[239,241,242]

Obestatin

Obestatin originates in the gastric mucosa of the stomach, the small intestine, and the pancreas, and is a posttranslational product of preproghrelin. Obestatin's function with energy homeostasis is to inhibit food intake, prevent body weight gain, and reduce gut motility.[243] Obestatin does not appear to affect expression in the brain of NPY, AgRP, and POMC, but it did inhibit ghrelin-induced expression of NPY and NPY receptors.[243]

Nesfatin

Nesfatin is found in the gut and hypothalamus as a neuropeptide. Its expression in the stomach and duodenum, as well as exogenous peripheral administration of the hormone, activates vagal afferent neurons to reduce food intake.[244-246]

As is evident, physiological actions for these molecules include altering feeding behaviors through central and peripheral actions. Much of this work has been shown in genetically altered animal models. Interestingly though, acute and/or chronic administration of these hormones as pharmacologic agents to increase their levels and actions may alter feeding behaviors, but several have inherent limitations reducing their application for obesity treatment in their current state. As described, CCK reduces meal size but demonstrates compensatory increases in meal frequency with no change in total daily food intake. Tolerance also develops with repeated CCK administration,[247] which may undermine its clinical utility. Furthermore, leptin administration to non–leptin-deficient animals, including humans, even at supraphysiological levels, is mostly ineffective in altering food intake and reducing body weight.[248] In some treatment programs with these hormones, nausea and gut distress accompanies their use.[161,249] A recent publication did show promise as a 10-hour subcutaneous infusion of a combination of GLP-1, PYY, and oxyntomodulin in obese adults decreased total daily ad libitum food intake by about 32% with no difference in sensations of hunger, amount to eat, and fullness as compared to a saline infusion.[250] Optimism for the use of gut hormone–derived treatments comes from specific targets of appetite controlling

systems and less likelihood of adverse side effects than current drugs.[251]

Altered Pathways in Obesity

Obesity and diabetes are commonly associated with resistance to or diminished production of peripheral and central regulators of energy homeostasis, including energy expenditure and food intake.[252] Disturbances in metabolic, neural, or hormone signals can occur with a number of metabolic disorders, such as obesity, anorexia nervosa, and diabetes. Vagal nerve actions are altered via neuropathy present in obesity and diabetes.[253] Research shows a reduction in responses to CCK and leptin at the vagal nerve in mice fed a high-fat diet.[254] The inflammation present in obesity may spread to the vagus nerve and then to the hypothalamus.[255,256] As circulating signals (glucose, triglycerides, hormones, and cytokines) are altered with obesity, this influences a number of factors that have a dysfunctional effect on fuel metabolism and energy homeostasis. These include central and leptin signaling and blood-brain barrier permeability.[149,257-260] With these altered responses to food intake signals, obesity may worsen.

Levels of gut peptides following a meal are attenuated in obese individuals, suggesting a dampened satiety response with eating.[236,261] Leptin resistance is characterized by high leptin levels and is apparent in obesity. There is a lower response to leptin's action in the arcuate nucleus, namely, with the POMC, NPY, and AgRP neurons.[262-264] This impaired function of leptin occurs experimentally with sustained exposure to high-fat diets.[265,266] During high-fat feeding, up to one fourth of the POMC neuronal population is lost,[266] leading to a dampened response to leptin and increased susceptibility to obesity. An upregulation of leptin receptor mRNA is observed with extended high-fat diet consumption.[265,267,268] Over time, desensitization of leptin signaling pathway occurs and leads to higher food intake and obesity.[265] Interestingly, administering melanocortin agonists makes mice with diet-induced obesity hyperresponsive, indicating that the melanocortin system is functioning properly downstream of the arcuate nucleus.[262]

Obesity Therapeutics

Intensive lifestyle treatments lead to about a clinically significant 7% to 10% weight loss at 1 year.[269] However, weight loss in primary care settings do not always achieve clinical significance (>5% weight loss). Sustaining behavior change for long-term weight loss maintenance is difficult based on biological and environmental challenges imposed. Thus, adjunctive therapy, such as including pharmacotherapy, may be necessary. Patients who have a history of unsuccessful prior attempts at weight loss and meet label indications are candidates for obesity pharmacotherapy. Ultimately, the initial goal with adjunctive pharmacotherapy to diet and exercise is to help patients achieve a weight loss of 5% or more, which has been shown to be sufficient in reducing significant health risk such as hypertension, impaired glucose tolerance, and nonalcoholic fatty liver disease.[270]

Soon after leptin was characterized, there was great interest in its potential use in treating human obesity. However, because congenital deficiency is rare in humans,[271] this excitement has waned. In the scarce cases of congenital leptin deficiency, individuals present with morbid obesity, profound hyperphagia, and type 2 diabetes.[272] For these individuals, daily leptin use lowers food intake, reduces body weight, and their diabetes is resolved, essentially reversing morbid obesity.[116] Unfortunately, research does not support the use of leptin alone for antiobesity therapy in obese individuals with leptin resistance.[248] However, a number of agents that restore leptin sensitivity have been investigated for their long-term effectiveness in obesity treatment. These pharmacological agents have targeted pathways that are known to affect leptin sensitivity: reducing endoplasmic reticulum stress, reversal of SOCS3 inhibition, and enhancing expression of leptin receptors.[273] Although these monotherapy approaches have not been highly effective, they do underscore the complexities with energy homeostasis and the regulation of feeding behaviors and energy expenditure. Promising results are found though when leptin is combined with other hormonal therapy, including CCK, amylin, and GLP-1; these polytherapies provide greater reduction in food intake and body weight than leptin alone.[274-277] Use of agents that improve leptin sensitivity along with leptin may also be a future therapy for obesity treatment.[278] Furthermore, antagonists to molecules that serve as endogenous negative regulators of leptin are being investigated to improve leptin sensitivity.[278-282]

Current Food and Drug Administration–approved medications for long-term treatment of obesity have demonstrated limited success in research trials. There are 4 medications with mechanisms that target central and peripheral hormonal and neural responses. Available agents for obesity treatment include lorcaserin, a selective 2C serotonin receptor agonist; liraglutide, an analogue of human GLP-1; and 2 combination preparations: phentermine, an adrenergic agonist, and topiramate ER, a neurostabilizer (Qysmia); and naltrexone ER, an opioid receptor antagonist, and burpropion SR, a dopamine and norepinephrine reuptake inhibitor (Contrave). Lorcaserin, which stimulates POMC neurons, showed in a 2-year follow-up a placebo-subtracted weight loss of over 3 kg.[283] Importantly, more patients lost at least 10% of initial body weight with lorcaserin than placebo.[284] Phentermine is available either alone or with topiramate and it works centrally through a catecholamine agonist (norepinephrine and dopamine). A low-dose version of phentermine (Lomaira) is marketed to curb evening appetite with minimal impact on sleep. Topiramate's weight loss action is unknown.[285] Bupropion inhibits the reuptake of dopamine and

norepinephrine and reduces appetite through stimulating POMC neurons. Naltrexone blocks the effect of beta-endorphins secreted from POMC neurons.[270] The placebo-subtracted weight loss was nearly 9 kg for phentermine and topiramate combination and 5 kg (4.8%) for the bupropion and naltrexone combination.[283] Liraglutide affects food intake through a central action of increased stimulation of POMC, and peripherally by increased vagal afferent stimulation.[286,287] More than a 5 kg (5.4%) difference in weight loss between placebo and liraglutide treatment groups have been shown.[283] Other agents that also are agonists to the GLP-1 receptor are being developed.[288,289] As is apparent, significant, albeit modest, reductions in weight are observed with current Food and Drug Administration–approved medications. Additionally, health care providers generally have inadequate training to utilize and counsel their patients on these medications.[290]

Several promising studies have utilized oxytocin as an antiobesity medication.[291] Administering oxytocin peripherally activates vagal afferent neurons and suppresses food intake through action on the nucleus tractus solitaris.[292] Therapeutically, receptor antagonists to melanin concentrating hormone have been studied in rodent models for potential antiobesity medication.[293,294] These antagonists show potential promise for an antiobesity medication as they lead to reduced food intake, lower consumption of palatable foods, and body weight loss in diet-induced obese mice and rats.[293,294]

Off-label use of medications for obesity prevention or treatment include bupropion, metformin, zonisamide, and pramlintide. Bupropion is a norepinephrine and dopamine reuptake inhibitor and it showed an average of an additional 2.8 kg of weight loss relative to placebo after 6 to 12 months of monotherapy treatment.[295] Metformin, the insulin sensitizer medication shows small, but a sustained 2% greater weight loss than placebo. Its use as an adjuvant to prevent or reduce weight gain with antipsychotic drugs shows promise.[296] Zonisamide, which is used to treat epilepsy, produced a greater than 3% weight loss than placebo at 12 months, but adverse side effects likely limit its general use.[297] The analogue of human amylin, pramlintide, showed an additional 2.2 kg of weight loss relative to placebo.[298]

Mice and humans with a deficiency or defect in MC4R demonstrate hyperphagia and obesity.[31,33] Conversely, exogenous agonists of MC4R, including setmelanotide, are being used in clinical studies as potential antiobesity therapy.[299,300] MC4Rs are involved in both sides of energy homeostasis with MC4Rs in the paraventricular hypothalamus and the amygdala involved in food intake control and neurons with these receptors in other locations of the brain regulate energy expenditure.[301] A recent study showed that an MC4R agonist increased resting energy expenditure in obese individuals, but did not affect exercise energy expenditure or the thermic effect of food.[299] In this short 3-day study, no adverse effects on blood pressure was observed, providing optimism for its long-term use in selected obese individuals.

Other centrally acting agents are being developed and tested for safety and efficacy. Mechanisms of action for these include antagonists to the NPY receptors and altering dopamine, serotonin, and norepinephrine with varying degrees of success.[300,302,303] Additional drugs and drug combinations that work either peripherally or with both central and peripheral actions are in various stages of research. These include drugs that (1) interfere with the digestion of nutrients (fats and carbohydrate), (2) alter the absorption of glucose from the intestine and the reabsorption of glucose in renal tubules, (3) inhibit production of capillaries in adipose tissue, (4) downregulating growth factors involved in fat storage, (5) increasing AMP activated protein kinase, (6) stimulators of the beta2 adrenergic receptor, and (7) mimetics of PYY, oxyntomodulin, and amylin and antagonists for ghrelin.[249,270,300,304-309]

Summary

Regions of the brain, primarily the hypothalamus and brain stem, integrate neural and hormonal signals from the periphery and other brain areas, to elicit feeding behaviors. These diverse messages from the periphery are in response to the body's energy status. As dysfunctions in these signals become apparent, especially observed in experimental animal models, obesity and eating disorders can ensue. The catabolic and anabolic neurons in the CNS, including NPY, AgRP, and POMC, are important in this process. The discovery of leptin opened the door to understanding how adipose tissue communicates with the CNS. Similarly, a number of gut hormones have been researched with promising results in manipulating their actions to help treat obesity. Although current therapies with pharmacologic agents have been mostly disappointing, further research in this area will likely lead to better agents with fewer side effects and greater efficacy.

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