

Central control of energy homeostasis

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Purpose of review

Obesity is a chronic disease characterized by an accumulation of excess adipose tissue and associated with an increased risk of multiple morbidities and mortality. Recent findings have provided a myriad of complex interrelationships between the central and peripheral control of energy homeostasis. This review aims to select and interpret the most influential and powerful recent literature.

Recent findings

A complex system of overlapping neuroendocrine control mechanisms maintains energy homeostasis and makes weight loss maintenance very difficult. Meal size, feeding initiation, and energy store status have all been shown to be controlled, at least in part, by various hormones and neural signals. The hypothalamus serves as the center for this crosstalk and biochemical modulation of energy homeostasis. Weight loss is associated with a change in concentrations of circulating levels of hormones that trigger the hypothalamic production of neuropeptides that induce hunger and decrease energy expenditure, and the suppression of molecules that inhibit food intake and increase energy expenditure.

Summary

A greater understanding of these complex networks of energy regulation systems will invariably lead to effective treatments for obesity and associated comorbidities such as type 2 diabetes.

Keywords

obesity, weight loss, food intake, leptin, energy homeostasis, neuroendocrine

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Abbreviations

AGRP	agouti-related protein
GLP	glucagon-like peptide
MCH	melanin-concentrating hormone
MSH	melanocyte-stimulating hormone
NPY	neuropeptide Y
POMC	proopiomelanocortin
PYY	peptide YY ₃₋₃₆

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Introduction

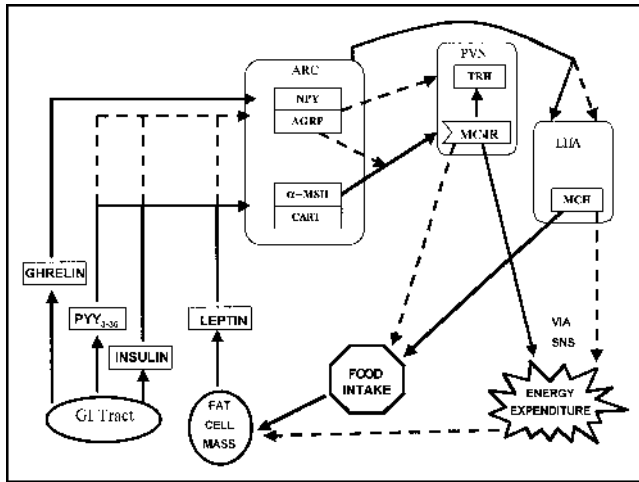
Obesity is a chronic disease characterized by an accumulation of excess adipose tissue and associated with an increased risk of multiple morbidities and mortality. Although originally misunderstood as a purely behavioral disorder, the discovery of the adipose tissue-derived hormone leptin in 1994 catalyzed the field of obesity research by demonstrating the existence of an afferent humoral signal from adipose tissue to the central nervous system. Current evidence suggests that a complex network of overlapping neuroendocrine systems is invoked when body fat mass is reduced, that acts to increase appetite and decrease metabolism in such a manner that maintenance of achieved weight loss becomes extremely difficult.

Regulation of energy homeostasis

Adipose-derived leptin circulates at levels proportional to body fat mass and activates signals in the hypothalamus that inhibit food intake and increase energy expenditure. Leptin administration induces weight loss in leptin-deficient mice; however, obese humans commonly have elevated circulating concentrations of leptin, and only a few individuals with severe obesity have been identified with either congenital leptin deficiency or a mutation in the leptin-receptor gene. Therefore, it has been suggested that obese persons are leptin resistant; perhaps because of a postreceptor defect in the transduction of its signaling through the janus kinase (JAK)-signal transducers and activators of transcription (STAT) pathway or stimulation of a member of the suppressors of cytokine signaling family (SOCS-3) that prevents activation of the JAK-STAT pathway [1]. During maintenance of a reduced body weight, however, administration of low-dose leptin reverses the decreases in energy expenditure and circulating concentrations of thyroid hormones that occur in both lean and obese individuals [2].

Leptin is known to affect the gene expression and secretion of both anorectic (appetite suppressing) and orexigenic (appetite stimulating) substances (Fig. 1). Neuropeptide Y (NPY) is a hypothalamic orexigenic peptide that increases food intake and decreases energy expenditure. The expression of NPY mRNA is inhibited by leptin. Melanin-concentrating hormone (MCH), an orexigenic peptide, is increased with fasting and leptin deficiency. Disruption of the MCH gene or administration of an MCH1 receptor antagonist results in hypophagia and leanness in rodents, whereas targeted disruption of the MCH receptor-1 results in hyperphagia and resis-

Figure 1. Interaction of some hormonal and neural pathways that regulate food intake and body fat mass



A decrease in fat cell mass is sensed in the arcuate nucleus (ARC) of the hypothalamus by a decrease in leptin concentration. Counterregulatory mechanisms are activated to conserve body fat: anorexigenic signals, such as α -MSH and cocaine- and amphetamine-regulated transcript, are suppressed; orexigenic signals, such as AGRP and NPY, are stimulated. Neurons from the arcuate nucleus project to the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA) to decrease TRH and increase MCH synthesis. These changes cause an increase in food intake and a decrease in energy expenditure via the sympathetic nervous system (SNS) that ultimately aim to restore fat cell mass in this setting. Gastric hormones similarly modulate these hypothalamic pathways. Solid arrows: stimulatory. Dashed lines: inhibitory.

tance to diet-induced obesity [3–5]. Glucagon-like peptide-1 (GLP-1) and neurotensin are peptides that inhibit the ability of MCH to induce eating. Leptin also downregulates endocannabinoids that act at cannabinoid receptors in the hypothalamus and stimulate food intake [6]. Conversely, leptin stimulates the expression of genes encoding anorexigenic peptides. α -Melanocyte-stimulating hormone (α -MSH), a peptide derived from proopiomelanocortin (POMC), and cocaine- and amphetamine-regulated transcript, are hypothalamic peptides expressed in the same subset of neurons within the arcuate nucleus of the hypothalamus that are positively regulated by leptin and produce anorexia.

The melanocortin system is under intensive investigation because of evidence in both rodents and humans of its control of energy homeostasis [7]. There are five different receptors for α -MSH, two of which (MC3R and MC4R) are primarily expressed in the hypothalamus [8]. Some of the metabolic effects resulting from stimulation of MC4R are decreased food intake and an increase in energy expenditure through stimulation of thyrotropin-releasing hormone and activation of the sympathetic nervous system. Targeted deletion of the MC4R gene produces obesity, hyperphagia, hyperinsulinemia, and reduced energy expenditure. Targeted deletion of MC3R results in increased adiposity caused by decreased energy expenditure [9••]. The central mel-

anocortin system also regulates insulin release and peripheral insulin responsiveness independently of its effects on feeding behavior and adiposity. Further evidence for the importance of the melanocortin pathway stems from the identification of agouti-related protein (AGRP). AGRP is a hypothalamic peptide that stimulates food intake in the rat through antagonism of the interaction of α -MSH at MC4R [10]. AGRP gene expression is suppressed by leptin. Melanocortin signaling may also be regulated by receptor desensitization and internalization [8].

Mutations in MC4R are found in approximately 1 to 7% of humans with a body mass index >40 and are particularly associated with severe early-onset obesity. These mutations signify the most prevalent identifiable monogenic defect that causes obesity. Reports of rare mutations in the genes for POMC and the enzyme that processes the POMC protein to α -MSH have surfaced as well and are associated with severe childhood obesity.

Other hypothalamic pathways influence feeding behavior, accumulation of body fat, and/or insulin sensitivity. Interference with central pathways involved in the synthesis of malonyl-CoA or fatty acids with either genetic knockouts of acetyl-CoA carboxylase or fatty acids synthase inhibitors (C75) decreases body fat [11–13]. Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and endogenous glucose production [14••]. These results suggest that rates of lipid oxidation in hypothalamic neurons relay nutrient availability information to the hypothalamus and thereby modulate food intake and insulin sensitivity. Targeted disruption of the histamine H3 receptor results in obesity in mice [15]. Localization of the receptor mediating the orexigenic effects of galanin (a peptide produced in the central nervous system, pituitary, gastrointestinal tract, and pancreas) has been reported [16]. Central administration of galanin-like peptide (a peptide produced in the hypothalamic arcuate nucleus, the median eminence, and the posterior pituitary) has been shown to invoke orexigenic actions similar to galanin, with dissimilar anorectic effects such as decreased intake and increased body temperature 24 hours after administration [17].

Gastrointestinal tissues relay energy balance information to the brain via neural and endocrine pathways. Growing evidence indicates that the central actions of insulin parallel those of leptin; central administration of insulin reduces food intake and body weight, whereas impairment of hypothalamic insulin receptors causes hyperphagia and insulin resistance [18•,19•]. A cooperative anorectic effect of leptin and insulin has been demonstrated by Niswender *et al.* [20••]: intracerebroventricular infusion with PI3K inhibitors (a signaling molecule responsible

for peripheral insulin action) impeded the anorectic effects of both intracerebroventricular leptin and insulin.

Another peptide, ghrelin, produced by the stomach, intestine, pituitary, and possibly hypothalamus, has been identified as an orexigenic peptide [21]. Intracerebroventricular injection of ghrelin stimulates feeding in the rat and increases body weight through stimulation of NPY and AGRP neurons. In a brown adipose tissue model, ghrelin stimulation greatly impaired adiponectin expression while selectively activating the mitogen-activated protein (MAP) kinase-signaling pathway [22]. Intravenous injection of ghrelin in humans induces subjective hunger and food intake. The preprandial rise and postprandial fall in plasma ghrelin levels and correlation with hunger indicate that ghrelin may play a role in meal initiation in humans. Weight loss induced by dietary fat restriction may prevent the rise in circulating ghrelin and fall in leptin concentrations that usually occur with caloric restriction [23].

Another gut hormone, peptide YY₃₋₃₆ (PYY), is an agonist of the NPY Y2 receptor expressed on NPY neurons in the arcuate nucleus that is released postprandially in proportion to the caloric content of a meal. Injection of PYY decreases NPY and increases POMC neuronal activity and reduces food intake in rodents and humans [24••]. Cholecystokinin (CCK), which is released in response to dietary fat, enhances nutrient absorption by slowing gastric emptying and stimulating gallbladder contraction, and it inhibits food intake during the meal via the afferent vagal system. Glucagon-like peptide-1 (GLP-1) inhibits gastrointestinal motility, hunger, and food intake. A deficiency of dipeptidyl peptidase IV, a member of the prolyl oligopeptidase family of peptidases, was shown to elevate GLP-1 levels and result in increased energy expenditure and reduced food intake [25•]. Secretion of gastric inhibitory polypeptide, a duodenal hormone, does not affect food intake but promotes obesity through efficient storage of nutrients as fat [26].

It has also been shown that the adipocyte-derived hormone adiponectin (also known as AdipoQ or Acrp30) increases fatty acid oxidation in muscle and liver and may regulate fat accumulation without significantly affecting food intake [27]. Many other molecules, including other peptides, neurotransmitters, cytokines, steroid hormones, and enzymes such as 11 β hydroxy steroid dehydrogenase that are involved in steroid hormone metabolism, affect energy homeostasis but are beyond the scope of this review.

Future therapeutic strategies

A myriad of new targets for obesity treatment has arisen from recent advances in our understanding of the complex circuitry controlling energy homeostasis. It appears

that orexigenic signals are redundant as a safeguard for survival. Thus, impairment of one signal, such as the knockout of AGRP, NPY, galanin, or ghrelin, does not produce any obvious metabolic disorder. Effective weight loss therapy will most likely involve blockade in the action of more than one orexigenic factor to yield a rational combined therapy.

Initially, the finding that circulating ghrelin concentrations are decreased in obese compared with lean humans suggested that the use of ghrelin antagonism as a treatment for common obesity may not be effective. However, ghrelin concentrations are decreased further after weight loss induced by gastric bypass surgery, as opposed to increased after diet-induced weight loss, suggesting that ghrelin antagonists may ameliorate hunger and aid in the maintenance of weight loss [28••]. In addition, ghrelin antagonists may be particularly effective in the treatment of obesity in patients with Prader-Willi syndrome who have several-fold higher concentrations of ghrelin than do equally obese control participants. The effect of such antagonists on growth hormone secretion will need to be elucidated.

Several drugs are currently in preclinical or clinical trials. One drug, rimonabant (Sanofi-Synthelabous, Great Valley, PA, USA), a CB₁ receptor antagonist, suppresses tonic endogenous activation of the orexigenic endocannabinoid system. Another, axokine (Regeneron Pharmaceuticals, Tarrytown, NY, USA), is an analog of ciliary neurotrophic factor that appears to activate the central leptin pathway distal to the leptin receptor. The effectiveness of axokine in promoting weight loss was limited, however, by the development of antibodies in a majority of the study participants [29•]. Other possible therapies include sustained-release bupropion, an antidepressant that is a dopamine and norepinephrine reuptake inhibitor, and the antiepileptic drugs topiramate (Ortho-McNeil, Raritan, NJ, USA) and zonisamide (Elan Pharmaceuticals, San Diego, CA, USA). Metformin (Bristol-Meyers Squibb Co, Princeton, NJ, USA), an agent approved by the US Food and Drug Administration for the treatment of type 2 diabetes, which inhibits hepatic glucose production, improves sensitivity to insulin, induces small weight loss, and reduces the risk of progression from impaired glucose tolerance to type 2 diabetes [30]. Inhibitors of tyrosine phosphatase-IB, an enzyme that appears to be involved in the mechanism of leptin resistance, have shown promise in preclinical studies. Stimulation of thermogenesis may become possible with the development of potent yet specific β_3 -adrenergic-receptor agonists. Interestingly, it has been shown that the anorexic action of d-fenfluramine, a serotonergic agent that was withdrawn from the market because of adverse cardiopulmonary events, requires activation of central melanocortin pathways, indicating that MSH analogs or drugs that target downstream melanocortin path-

ways may be effective without incurring serotonin-associated side effects.

Conclusion

It is clear that established obesity is a multiorgan endocrinopathy of body weight regulation strongly mediated by the central nervous system. Future therapies should specifically target elements within the weight control circuitry that will maximize efficacy, perhaps when used in combination, but will not result in the problematic side effects associated with past and present treatments.

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