Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2010 October ; 17(5): 441–445. doi:10.1097/MED.0b013e32833c3013.

Molecular neuroendocrine targets for obesity therapy

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Abstract

Purpose of review—Although energy balance is tightly regulated in order to maintain a specific level of adiposity, the incidence of obesity continues to increase. Consequently, it is essential that effective therapeutics for the treatment and prevention of obesity be developed. This review provides a brief update on some recent advances in the characterization of neuroendocrine targets for obesity therapy.

Recent findings—During the review period, considerable progress occurred in the understanding of previously-described neuroendocrine regulators of energy balance, and several novel targets have been identified. Moreover, the understanding of the neural circuitry and molecular mechanisms of neuroendocrine regulators of energy homeostasis has been expanded.

Summary—Energy balance is maintained by neuroendocrine signals arising from many tissues including the gastrointestinal tract and adipose tissue. These signals are integral to the cessation of meals and to the ability of the brain to monitor energy status and respond accordingly. Many current targets for obesity therapy are based on manipulating the activity of these signals and their receptors; however, to date, clinical weight loss based on this strategy has been minimal and alternative approaches such as combinatorial therapies are emerging.

Keywords

Obesity; food intake; neuroendocrine; metabolism; energy balance

Introduction

In spite of a robust regulatory system that defends a particular level of adiposity, the prevalence of obesity continues to increase [1, 2]. The origin of this apparent dysregulation with its enhanced susceptibility to excessive weight gain is complex and likely due to many environmental factors including an increased availability of calorically dense foods and reduced average physical activity. Interestingly, recent evidence suggests that enhanced susceptibility to life-long weight-gain is also influenced by factors of the intrauterine environment, including maternal obesity and stress [3*]. Social and environmental factors, including time of day, food availability and palatability, stress and physical activity, are integral components in the feeling of hunger and initiation of meals [4*]. Other factors, including neuroendocrine signals originating from many tissues including the central nervous system (CNS), the gastrointestinal system and adipose tissue, are important for the cessation of meals (satiation signals) and the coordination of caloric intake with maintenance of stable body weight. Many of the current targets under investigation as

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The authors have nothing to disclose.

obesity therapeutics are based on manipulating one or multiple (combination therapies) of these neuroendocrine signals. In this review, we provide an update on some of the recent advances in the characterization of several molecular neuroendocrine targets for obesity therapy and the underlying mechanisms pertinent to the control of energy balance.

Short-term regulation of food intake: satiation signals

Rather than being caused by neuroendocrine signals heralding a deficit of energy stores, meal initiation is under the control of environmental factors, learning/habits and opportunity [4]; conversely, neuroendocrine factors have a major influence on the amount eaten once a meal begins. During a meal, signals are generated in response to the ingested nutrients, signals that coordinate the digestion and absorption of the meal, as well as generating a feeling of fullness. These short-term regulators of food intake are collectively called satiation signals, and many of them have been evaluated as potential therapeutic agents for obesity.

Cholecystokinin (CCK)

CCK is the prototypical example of a short-term satiation factor. CCK is released by intestinal I-cells in response to ingested lipids and other nutrients, and it stimulates the liver and pancreas to secrete digestive enzymes and also activates receptors on vagal afferent nerves to reduce meal size [5-7]. Exogenous CCK reduces meal size in animals and humans, and blocking its receptors results in larger meals [8-10]. That said, there is evidence that chronically administering CCK does not reduce body weight [8, 11] due in part to compensatory increases in meal frequency [8] and to a loss of efficacy of CCK's ability to reduce meal size [12]. Some studies indicate that long-acting formulations of CCK can produce sustained reductions of food intake [13], but even these long-acting CCK receptor agonists do not produce weight loss in a clinical setting [14]. Additionally, mice lacking CCK are resistant to diet-induced obesity [15*], further implying that CCK may not be an ideal candidate for obesity therapy.

Glucagon-like peptide 1 (GLP-1)

GLP-1 is a peptide secreted by intestinal L-cells during a meal and is also made within the brainstem [16, 17]. Plasma GLP-1 increases during meals and its best-known action is as an incretin (i.e., it enhances prandial insulin secretion) [18]. Although exogenous GLP-1 reduces food intake [19, 20*, 21], the relationship between GLP-1 and meals is complex. It is secreted in anticipation of meals [22*] as well as in response to ingested nutrients [18]. Like CCK, gut-derived GLP-1 signals the brain via the vagus nerve [23], and there is evidence that this gut-derived GLP-1 acts both peripherally and centrally to reduce food intake [20*, 21, 24-26]. Central administration of GLP-1 agonists reduces food intake whereas antagonists produce the opposite effect [20*, 27].

Because GLP-1 is rapidly degraded by the enzyme, dipeptidyl-peptidase-4 (DPP-4), clinically active compounds targeting the GLP-1 system include DPP-4 inhibitors and DPP-4-resistant GLP-1 receptor agonists, and formulations of both are currently approved for clinical use for treating type-2 diabetes. Interestingly, the administration of GLP-1 agonists but not DPP-4 inhibitors is associated with weight loss in a clinical setting [28, 29*], and it has been hypothesized that increased GLP-1 activity might contribute to weight loss following bariatric surgery [30].

Ghrelin

Ghrelin is a peptide secreted mainly by the stomach that stimulates food intake and can promote adiposity. Ghrelin is a unique peptide in requiring an attached (acylated) fatty acid

(octanoate) to become active [31, 32]. Ghrelin *o*-acyl transferase (GOAT), the enzyme responsible for ghrelin's acylation, is the subject of intense scrutiny since it is regulated by nutrient availability, and especially by the presence of certain dietary lipids [33, 34**]. It has been hypothesized that GOAT serves as a link between lipid availability and the neuroendocrine regulation of energy balance [34**].

Other neuroendocrine satiation signals

Numerous other short-term regulators of food intake are under consideration as targets for treating obesity. Most share the properties of being made in organs of the digestive system as well as in the brain, being secreted during meals, and reducing acute food intake when exogenously administered (see review in [28]). This includes amylin (reviewed in [35]), which is co-secreted with insulin from pancreatic B-cells and reduces meal size by acting directly in the brainstem [36, 37]. Synthetic formulations of amylin are approved as adjunct treatments for type-2 diabetes, and their use leads to weight loss in humans [38]. Peptide YY (PYY) is co-secreted from L-cells with GLP-1 and reduces food intake in humans and animal models [39]. While many neuroendocrine factors reduce food intake in acute studies, targeting their receptors in order to cause weight loss may not prove efficacious since numerous factors such as learning often intervene to thwart changes of body weight [4*].

Long-term regulation of energy balance: adiposity signals

Adiposity signals are circulating neuroendocrine factors that communicate the level of energy stores to the brain. They arise from several tissues, including pancreatic B-cells and adipose tissue. The two most-studied adiposity signals are insulin and leptin, and each is secreted in direct proportion to body fat, thereby communicating energy stores to the brain in an endocrine fashion. The brain in turn responds to these signals by adjusting energy intake and expenditure to maintain energy homeostasis. Consistent with this, administering either leptin or insulin directly into the brain reduces food intake and body weight, while reducing their activity in the brain produces the opposite effect [1, 2]. Caveats to targeting these hormones for obesity therapy include that although they are effective in normal-weight animals, obese individuals develop both leptin and insulin resistance; and that to be effective, the compounds might have to be administered directly into the brain. Amylin is also an adiposity signal in that like insulin it is secreted in proportion to body fat, and that manipulating its activity locally in the brain leads to changes of body weight [36].

Another potential adiposity signal derives from the renin-angiotensin neuroendocrine system and its active end-product, angiotensin-II (reviewed in [40]). Although angiotensin-II is best-known for increasing blood pressure and blood volume, it is also synthesized in adipose tissue in direct proportion to the amount of stored fat [40]. Adipose-derived angiotensin-II facilitates adipose tissue expansion and acts systemically to contribute to obesity-related hypertension and diabetes [40]. We have found that increased angiotensin-II activity in brain promotes negative energy balance, consistent with its being an adiposity signal [41*, 42].

Brain factors in the neuroendocrine regulation of energy balance

Energy homeostasis is influenced by a multitude of environmental, learned, social, hedonic and other factors in addition to those related to energy stores per se (i.e., in addition to homeostatic factors) [4*, 43]. Hence, a comprehensive analysis of the neural circuits, neurotransmitters and other brain factors that contribute to energy balance is complex and beyond the scope of this review; rather, we focus on homeostatic signals and a few key brain areas. Neurons in the hypothalamic arcuate nucleus (ARC) receive information concerning satiation and also express receptors for most adiposity signals. One population of ARC neurons expresses anabolic neuroendocrine signals that stimulate food intake and body

weight, including agouti-related peptide (AgRP) and neuropeptide-Y (NPY), and another population expresses proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) [1], neuropeptide systems that are mainly catabolic. ARC neurons are also sensitive to circulating nutrients including glucose [44], fatty acids [45] and some amino acids [46], and these, in turn, are thought to influence the relative levels of two intracellular energy-sensing signaling systems, adenosine monophosphate-activated protein kinase (AMPK) and mammalian-target-of-rapamycin (mTOR) [46, 47]. ARC AMPK activation is indicative of low energy and elicits increased food intake, whereas ARC mTOR activation heralds energy excess and causes decreased food intake [46, 47], and the output of ARC neurons reflects the integrated information from satiation, adiposity and nutrient signals.

The ARC projects to several brain areas including the hypothalamic paraventricular (PVN) and lateral (LH) regions. The PVN regulates neuroendocrine responses to stressors and is a major determinant of autonomic tone and energy expenditure. Of relevance here, some PVN neurons synthesize anorexigenic factors including corticotrophin-releasing hormone (CRH) and oxytocin that project throughout the brain and act to reduce food intake and body weight [1, 2]. The LH on the other hand expresses the orexigenic peptides, melanin-concentrating hormone (MCH) and orexin [1, 2]. The important point is that several regions of the mediobasal hypothalamus, including the ARC, PVN, LH and others, integrate information concerning immediately available nutrients, tissue needs, energy stores and the state of ongoing meals and ultimately are a major factor in determining when meals are initiated and how much is eaten [4*].

The outputs of these hypothalamic circuits project throughout the brain including to the mesolimbic dopamine system which determines among other things the hedonic or reward properties of foods [48**], and to areas in the brainstem that directly control autonomic activity, gastrointestinal function and the physical act of eating. The nucleus-of-the-solitary-tract (NTS) in particular is a major brainstem integrative area, receiving direct sensory information regarding taste and neural and endocrine signals from throughout the gastrointestinal system, as well as the inputs from the hypothalamus. The NTS and other brainstem areas are also directly sensitive to adiposity signals such as leptin. For example, utilizing an adeno-associated virus, Hayes *et al.* knocked down leptin receptors in the NTS region and elicited chronic hyperphagia and increased body weight and adiposity [49**], in part through influencing local AMPK activity [49**, 50]. The NTS is also the brain area where estrogen influences the action of satiation signals such as CCK to cause a greater reduction of food intake [51].

The circumventricular organs are brain areas with a relaxed blood-brain barrier where neurons can directly sample hormones, nutrients and other circulating factors important in the neuroendocrine control of energy balance. For example, the area postrema, which is situated just above the hindbrain NTS, mediates the actions of amylin [36]. The subfornical organ is dorsal to the hypothalamus in the forebrain and projects directly to many of the nuclei controlling energy homeostasis [52]. Among many other neuroendocrine signals, it directly senses insulin, angiotensin-II and leptin [53*, 54*].

Other approaches

An important point is that there are several layers of neuroendocrine control over energy homeostasis, and that this redundancy makes it difficult to influence body weight by targeting only one or another piece of the system since others can become activated as a compensatory response and thwart attempts at long-term therapy. Moreover, there is evidence that the ability of many of these neuroendocrine regulators of energy balance to

decrease energy intake depends on learned associations between endogenous levels of the factors and the nutrient status [4*, 12]. When this occurs, pharmacological manipulation of these targets will result in a dissociation between the signal and nutrient status and hinder the effectiveness of the treatment (reviewed in [4*]). Nonetheless, alternative approaches to obesity therapy are being explored which manipulate neuroendocrine signals in novel ways.

One approach is combinatorial therapy, in which two or more pharmacological systems are simultaneously targeted with a goal of attaining an additive or perhaps even synergistic reduction of body weight. As an example, fen-phen was a therapeutic that combined compounds targeting different levels of control, and while it had deleterious side effects in some people, it nonetheless produced clinically meaningful weight loss [55]. More recently, administration of a glucagon/GLP-1 co-agonist reduced body fat and improved glucose tolerance in diet-induced obese mice [56*]. Analogously, combinations of formulations of amylin and leptin produce a synergistic reduction in body weight and adiposity that is more effective than either monotherapy in a clinical setting [57**].

The incidence of bariatric surgery is rapidly increasing, in large part because it effectively reduces weight and greatly lessens symptoms of diabetes [10, 58]. Importantly, there is evidence that commonly-applied bariatric surgical techniques work, at least in part, by influencing neuroendocrine signals such as GLP-1, ghrelin or others [59*, 60].

Understanding the impact of bariatric surgery on neuroendocrine regulation is a major research focus and may aid in uncovering less-invasive approaches for manipulating the same neuroendocrine signals without the need for surgical intervention.

Conclusion

Despite the ability of the neuroendocrine system governing energy balance to precisely regulate energy intake and expenditure in order to defend a certain level of adiposity, obesity is becoming a global health concern. Neuroendocrine signals arising from the gut, adipose tissue and other tissues play integral roles in maintaining energy stores, and many of the efforts to develop therapeutics to treat and prevent obesity have focused on manipulating these signals individually. Oftentimes, these manipulations have led to reductions in food intake and adiposity; however, these effects are modest. In order to develop more effective therapeutics, researchers are investigating the utility of combining therapies as well as the impact of bariatric surgery on the neuroendocrine regulation of energy balance.

Acknowledgments

We thank Dr. Eric Krause for his valuable advice and assistance. The preparation of this review was supported by National Institute of Health grants DK017844 and F31NS068122.

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