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Neuropeptides in the Pathophysiology and Treatment of Cachexia

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Abstract

Purpose of review—Cachexia occurs in various inflammatory diseases and is characterized by weight loss and muscle wasting. Pro-inflammatory cytokines modulate the activity of neuropeptides and hormones that control energy homeostasis and/or illness behaviors. This review summarizes recent (published within the past 18 months) literature regarding neuropeptides and hormones that have been implicated in the pathophysiology of cachexia, and that are likely to have therapeutic potential for preventing or reversing cachexia in various disease states.

Recent findings—Hypothalamic proopiomelanocortin (POMC) and agouti-related protein (AgRP) neurons are downstream targets for pro-inflammatory cytokines. Genetic or pharmacological blockade of melanocortin receptor signaling preserves lean body mass and attenuates anorexia in experimental models of cachexia. Orally available melanocortin receptor antagonists have been developed and tested in cachectic animals with favorable results. Ghrelin and ghrelin mimetics increase appetite and preserve lean body mass in cachectic patients with diverse underlying diseases. Additional neuropeptide-expressing neurons in the hypothalamus (e.g., orexin neurons) might play a role in cachexia-associated lethargy.

Summary—Promising outcomes from recent preclinical studies and/or early clinical trials with melanocortin receptor antagonists and ghrelin mimetics raise hopes that safe and effective anti-cachexia drugs for widespread clinical use are on the not too distant horizon.

Keywords

Cachexia; inflammation; melanocortin; ghrelin; cytokines

Introduction

Cachexia, or disease-associated wasting, is a metabolic disorder that has a profound negative impact upon morbidity, mortality, and quality of life. Cachexia occurs in many infectious and chronic diseases (e.g., acquired immunodeficiency syndrome, cancer, congestive heart failure, and chronic kidney disease) [1-4]. Cachexia was recently defined as “a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass” [5 (p. 794)]. In addition to the characteristic weight loss (in adults) or growth failure (in children), cachectic individuals commonly exhibit anorexia,

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increased resting energy expenditure, and lethargy. Nutritional intervention alone is insufficient to restore lean body mass in cachectic patients [6], and effective pharmacological treatments that prevent or reverse the symptoms of cachexia have so far remained elusive.

Cytokines and Peripheral Inflammation

The etiology of cachexia is multifactorial, involving complex interactions between immune, metabolic, endocrine and neural mediators. Inflammation is believed to play a causal role in the pathogenesis of cachexia across diverse disease states [7]. Cachexia is associated with elevated circulating levels of pro-inflammatory cytokines [e.g., interleukin-1β (IL-1β), interleukin-6, tumor necrosis factor-α (TNF-α) and leukemia inhibitory factor (LIF)] in humans [8,9]. Pro-inflammatory cytokines, which are released by peripheral immune cells in response to infection or tissue damage, act upon their target cells in a paracrine or endocrine manner. Although pro-inflammatory cytokines can promote catabolism via direct effects on skeletal muscle and adipose tissue *in vitro* [10,11], many of the metabolic and behavioral actions of pro-inflammatory cytokines have been attributed to cytokine signaling within the central nervous system (CNS).

Cytokines and Central Inflammation

Systemic inflammatory responses are amplified by the local production of pro-inflammatory cytokines within the CNS [12]. These brain-derived cytokines act upon neural circuits in the hypothalamus and brainstem that modulate energy homeostasis, hormone secretion, and autonomic function [13*]. Acute inflammatory stimuli activate nuclear factor kappa B (NF-κB, a transcription factor upon which many inflammatory signaling pathways converge) [14] and induce expression of the immediate early gene *c-fos* (a marker of neuronal activation) [15] in discrete hypothalamic and brainstem nuclei. The bacterial endotoxin lipopolysaccharide (LPS) elicits profound anorexia in wild-type mice; however, a sustained LPS-induced reduction in feeding is not observed in mice with genetically disrupted inflammatory signaling pathways, not even in animals that are transplanted with wild-type circulating immune cells [16]. Collectively, these observations suggest that central inflammation plays a critical role in illness-induced pathophysiology.

In rodents, intracerebroventricular (ICV) cytokine administration recapitulates many of the features of cachexia [17-20]. Rats that received daily ICV injections of TNF-α for 4 days exhibited reduced food intake and body mass, increased oxygen consumption, and enhanced brown adipose tissue thermogenesis compared to saline-treated animals [21*]. Blockade of hypothalamic TNF-α signaling with infliximab increased food intake in tumor-bearing rats, partially restored body weight in rats with experimentally-induced sepsis, and improved survival in both experimental models of cachexia, thus lending support to the hypothesis that central cytokine signaling plays an obligatory role in cachexia.

Many neuropeptide-expressing neurons in the hypothalamus and brainstem participate in the control of feeding and metabolism. Some of these same neurons are responsive to inflammatory challenges. This review will highlight some of the neuropeptides and peptide hormones that modulate energy homeostasis and/or sickness behaviors, and that have also been implicated in the pathophysiology of cachexia. More importantly, many of these neural/endocrine mediators have been identified as promising therapeutic targets for the prevention and treatment of cachexia of various etiologies.

Melanocortins

The hypothalamic arcuate nucleus (ARC) is an important target for pro-inflammatory cytokines. The ARC contains two anatomically distinct populations of neurons that have opposing effects on energy homeostasis. One set of neurons produces α-melanocyte-stimulating hormone (α-MSH), an anorexigenic neuropeptide that is derived from the proopiomelanocortin (POMC) precursor. POMC neurons also reside in the nucleus of the solitary tract in the brainstem. α-MSH inhibits feeding and increases energy expenditure by activating melanocortin receptors, primarily the type 4 melanocortin receptor (MC4-R) [22]. A second population of neurons in the ARC secretes the orexigenic peptides neuropeptide Y (NPY) and agouti-related protein (AgRP). AgRP stimulates feeding and decreases metabolism by acting as an inverse agonist at the MC4-R [23].

POMC and AgRP neurons in the ARC are responsive to pro-inflammatory cytokines. Both POMC and AgRP neurons express the type I interleukin-1 receptor, and IL-1β stimulates α-MSH secretion and inhibits AgRP release from hypothalamic explants [24,25]. Interleukin-7 increases POMC mRNA in fed mice and reduces AgRP gene expression in mice that are re-fed for 4 hours following an overnight fast [26*]. Grossberg *et al.*, recently demonstrated that POMC neurons are direct targets for central LIF signaling [27**]. ARC POMC neurons express LIF receptor mRNA and are transcriptionally activated by central LIF treatment. Acute ICV LIF injection transiently suppresses food intake in wild-type mice and stimulates α-MSH secretion from wild-type hypothalamic explants. Transgenic mice that lack gp130 (the signal transducing subunit of the LIF receptor complex) only in POMC neurons exhibit attenuated LIF-induced α-MSH secretion and lack an anorectic response to ICV LIF treatment. Thus, intact LIF receptor signaling in POMC neurons is necessary for acute LIF-induced anorexia in mice. It remains to be determined whether a sustained activation of POMC neurons by chronically elevated LIF (or IL-1β) concentrations in the brain is necessary or sufficient to produce anorexia in the setting of chronic inflammation.

Relatively little is known regarding the intracellular signaling mechanisms by which inflammatory mediators activate POMC neurons. Jang and colleagues investigated the role of NF-κB activation in POMC neurons during acute inflammatory challenges [28**]. LPS, IL-1β and TNF-α stimulate transcription of the POMC gene *in vitro*; inhibiting NF-κB expression or activity attenuates or abolishes this effect. Transgenic mice that lack IκB kinase-β (an enzyme upstream of NF-κB activation) specifically in POMC neurons exhibit blunted anorexia and less weight loss in response to intra-hypothalamic LPS injection. Based on these observations, we can conclude that acute inflammation-induced anorexia and weight loss depend upon NF-κB-mediated transcription in hypothalamic POMC neurons. Although the authors of this study focused on acute illness in their experiments, it would be interesting to ascertain whether mice with impaired NF-κB signaling in POMC neurons resist developing anorexia/cachexia when exposed to a chronic inflammatory insult.

Genetic or pharmacological blockade of MC4-R signaling ameliorates cachexia in many animal disease models, including acute LPS administration, cancer, and renal failure [29-31]. Scarlett and colleagues extended these findings to two experimental models of cardiac cachexia [32*]. Unlike sham-operated controls, wild-type mice that underwent surgery to induce myocardial infarction (MI) failed to gain body weight, lean body mass or fat mass. In contrast, mice with a targeted deletion of the MC4-R gene gained body weight, lean body mass and fat mass regardless of whether they were in the sham-operated or MI groups. Furthermore, MI reduced food intake and increased oxygen consumption in wild-type mice but not in MC4-R null mice. In an aortic banded rat model of pressure overload cardiac hypertrophy, ICV AgRP treatment for 2 weeks increased body weight, lean body mass, fat mass and food intake compared to baseline values. The observation that chronic

blockade of central MC4-R signaling protects animals from developing cardiac cachexia suggests that MC4-R antagonism might be a viable therapeutic strategy for patients with chronic heart failure (CHF). Because pre-existing cachexia predicts mortality following heart transplantation, pharmacological MC4-R antagonism might be an effective pre-transplant therapy [33].

Preclinical studies utilizing small molecule, peripherally-administered MC4-R antagonists have yielded favorable results with respect to preventing or reversing anorexia and loss of lean mass in experimental models of acute and chronic illness [34]. Recently, MC4-R antagonists with oral bioavailability have been developed and tested in cachectic animals [35]. Weyermann et al., reported that SNT207707 and SNT207858 are novel, non-peptide, selective MC4-R antagonists that penetrate the blood brain barrier [36**]. Oral administration of these compounds dose-dependently increases food intake in healthy mice. In mice implanted with a C26 adenocarcinoma, once daily oral administration of SNT207707 and SNT207858 for 2 weeks prevents tumor-induced loss of body weight, fat mass, and lean body mass without affecting tumor size. It is unknown whether the preservation of body weight in the tumor-bearing mice was solely attributable to the orexigenic activity of the MC4-R antagonists, or whether SNT207707 and SNT207858 also alter metabolism and/or energy partitioning.

Monoclonal antibody therapy is another potential anti-cachexia therapeutic strategy. mAb 1E8a is selective for the human MC4-R and behaves as an inverse agonist and noncompetitive antagonist *in vitro* [37*]. Acute ICV injection of purified mAb 1E8a increases body weight and food intake in rats. Chronic (7 day) ICV infusion of mAb 1E8a stimulates food consumption, reduces weight loss and increases adiposity. A single chain variant of mAb 1E8a that crosses the blood brain barrier is effective at increasing food intake when administered intravenously.

To date, there have not been any published clinical trials with drugs that antagonize or impair MC4-R signaling. Given the recent promising results obtained from preclinical studies, it is presumably only a matter of time before the safety and efficacy of MC4-R antagonists are tested in human subjects.

Neuropeptide Y (NPY)

NPY is an orexigenic peptide that is co-expressed in the same neurons as AgRP in the ARC [38]. Like AgRP, NPY mRNA expression increases during states of energy deficiency (e.g., starvation), and centrally-administered NPY promotes feeding and weight gain [39]. NPY gene expression is usually either unchanged or increased in experimental models of chronic inflammation. For example, in a rat model of adjuvant arthritis, NPY mRNA levels were elevated despite reduced food intake, body weight and adiposity compared to control animals [40]. Repeated intra-hypothalamic NPY injections do not increase food intake in tumor-bearing rats, indicating desensitization to NPY in these animals [41]. Although some degree of dysfunction in the NPY system probably occurs in cachectic humans, cachexia does not appear to be an NPY-deficient state, and thus NPY replacement is unlikely to prevent or reverse cachexia in a clinical setting. Consequently, interest in NPY as an anti-cachexia therapy has waned over the past several years.

Ghrelin

Ghrelin is an orexigenic/anabolic peptide hormone that was identified by virtue of its ability to stimulate growth hormone (GH) secretion [42]. Ghrelin, which is primarily produced by neuroendocrine cells of the gastric fundus, is an agonist at the growth hormone secretagogue-1a (GHS-1a) receptor. Circulating ghrelin exists in two forms: acylated ghrelin

(the biologically active form that binds and activates GHS-1a receptors) and des-acyl ghrelin (an inactive form that lacks biological activity at GHS-1a receptors) [43]. Ghrelin is a meal initiation signal, with its plasma levels rising in the fasted state and decreasing post-prandially. Acute intravenous ghrelin administration increases caloric intake in humans [44], and chronic ghrelin treatment increases adiposity in mice [45]. NPY/AgRP neurons in the ARC express GHS-1a receptors [46], and both neuropeptides play essential roles in ghrelin-induced food intake [47]. In addition to its effects on energy homeostasis, ghrelin also exerts potent anti-inflammatory actions, at least in part, by decreasing peripheral immune cell expression of pro-inflammatory cytokines [48].

Although one recent study reported reduced plasma ghrelin concentrations in cancer patients [49], cachexia is more frequently associated with increased circulating ghrelin levels compared to healthy control subjects or non-cachectic patients with the same underlying diseases [50-53]. In rats, plasma ghrelin concentrations are transiently reduced following acute LPS administration but are increased by repeated LPS injections [54]. In the context of cachexia, increased plasma ghrelin concentrations could represent a compensatory orexigenic/anabolic response to tissue wasting. Alternatively, elevated ghrelin concentrations in cachectic individuals might signify a state of ghrelin resistance. Many human subject experiments only report total circulating ghrelin levels (i.e., the investigators do not distinguish between acylated vs. des-acyl ghrelin), and thus it is difficult to draw meaningful conclusions about levels of bioactive ghrelin in those patients. Nevertheless, the bulk of the evidence suggests that cachexia is not a ghrelin-deficient state.

In rodent models of cancer, kidney disease and CHF, administration of ghrelin or GHS-1a receptor agonists ameliorates many of the symptoms of cachexia [55-57]. In a rat model of CHF, repeated injections or chronic infusion of human ghrelin for 4 weeks elicited dose-dependent stimulatory effects on feeding, body weight gain, adiposity, and lean body mass accumulation, in the absence of any significant improvement in cardiovascular function [58*]. Skeletal muscle mitochondrial oxidative capacity is impaired in rats with chronic kidney disease but is corrected by ghrelin treatment, even in the absence of ghrelin-induced increases in food intake [59*].

Early clinical trials with ghrelin or synthetic ghrelin mimetics have shown increased caloric intake, body weight, and lean body mass in cachectic patients with various cancers, chronic kidney disease, congestive heart failure, and chronic obstructive pulmonary disorder [60]. Ghrelin has a short half-life (30 minutes) in the circulation and must be injected, both of which limit its utility as a therapeutic agent. Phase I and II clinical trial with the orally available, synthetic ghrelin mimetic RC-1291 have demonstrated increases in body weight and lean body mass in healthy subjects [61] and in cancer patients [62], without any dose-limiting side effects. Ghrelin's ability to stimulate the secretion of GH (and thus, insulin-like growth factor-1) raises the concern that ghrelin mimetics might increase tumor growth in cancer patients. To date, there have not been any published randomized, placebo-controlled clinical trials investigating outcomes of long-term treatment with ghrelin analogues in cachectic patients. Until these trials are performed, we can only speculate as to whether long-term administration of ghrelin analogues would elicit sustained increases in caloric intake and body mass accrual in cachectic individuals.

Orexins/Hypocretins

Orexin (also known as hypocretin) neurons in the lateral hypothalamus regulate feeding behavior, arousal, and motivated behaviors. Central administration of orexin-A acutely stimulates feeding but does not elicit sustained increases in feeding or body weight during chronic administration in rats [63,64]. Injection of orexin-A into the ventromedial

hypothalamus stimulates glucose metabolism and increases insulin sensitivity in skeletal muscle via activation of the sympathetic nervous system [65**]. Because orexins promote wakefulness and increase locomotor activity [66], it is conceivable that a sustained reduction in orexin neuronal activity might underlie lethargy in cachectic individuals. However, the response of orexin neurons to an acute inflammatory challenge is equivocal. In rats, peripherally-administered LPS either increases or decreases Fos expression in orexin neurons during the dark phase of the light/dark cycle, which is when orexin neurons are maximally activated [67*,68]. In pilot studies, the psychostimulant modafinil (which stimulates orexin neurons) reduced fatigue in cancer patients [69*,70*]. A potential role for orexins in the pathophysiology of cachexia remains largely unexplored.

Conclusions

Cachexia is characterized by a profound dysregulation of metabolic function. The neural mechanisms contributing to the pathophysiology of cachexia are complex, and as such remain poorly defined. Safe and effective pharmacological treatments for cachexia are currently lacking, but randomized, placebo-controlled clinical trials with MC4-R antagonists or long-term treatment with ghrelin mimetics are eagerly anticipated. Although most researchers in the cachexia field study muscle catabolism and/or appetite regulation, it is important not to ignore the negative impact of other cachexia-related symptoms (e.g., lethargy). Elucidating the mechanisms by which inflammatory mediators promote muscle wasting, anorexia and other illness behaviors will not only shed light upon the basic biology of cachexia and its underlying disease processes, but will also hopefully identify novel therapeutic strategies for treating cachexia of various etiologies.

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