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Review

Ghrelin and cachexia: Will treatment with GHSR-1a agonists make a difference for patients suffering from chronic wasting syndromes?☆

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ABSTRACT

Cachexia is a syndrome of wasting and anorexia that worsens the prognosis of many chronic diseases including cancer, chronic kidney disease, chronic heart disease and chronic obstructive pulmonary disease. Properties of the orexigenic hormone ghrelin-including appetite-stimulation, weight-gain production and increased cardiac output make it a logical treatment for cachexia. While endogenous ghrelin levels are increased in the setting of cachexia, treatment with ghrelin and other GHSR-1a agonists in animal models of cachexia and in humans with cachexia has demonstrated consistent effects of increased appetite and improved weight gain. These positive effects occur in multiple underlying diseases associated with cachexia and appear to be sustained over treatment duration of up to 12 weeks. The mechanism of action in producing these effects is likely related to stimulation of central appetite centers such as the central melanocortin system and to increased growth hormone release, though ghrelin's effects may also relate to decreased systemic inflammation and other direct and indirect actions. Questions regarding the long-term safety of ghrelin treatment are still unanswered, as is the important question of whether successful treatment of cachexia will improve the prognosis of the underlying disease itself.

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1. Introduction

Cachexia is a wasting syndrome that accompanies a wide array of chronic diseases including cancer, chronic kidney disease, chronic heart disease and chronic obstructive pulmonary disease (COPD) (Tisdale, 1997; Evans et al., 2008). While these diseases are varied in their underlying pathophysiology, they each result in a loss of lean and fat mass that is in part fueled by an increase in resting energy expenditure. Perhaps the most striking characteristic of cachexia, however, is on-going anorexia at a time when energy stores are depleted. Thus far, no definitive treatment has been shown to be effective for use in humans with cachexia.

One agent that has gained attention as a potential treatment for cachexia syndromes is the gut hormone ghrelin (Kojima et al., 1999; Tschop et al., 2000; Nakazato et al., 2001). Given its properties of increasing appetite and increasing fat mass accumulation—that is, the opposite of processes observed during cachexia—ghrelin has been investigated in a growing number of animal models and human trials testing its efficacy in treating cachexia. As we will see in this review, ghrelin and other agonists of the growth hormone

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secretegogue receptor (GHSR-1a) also exhibit additional properties that may further benefit specific underlying diseases associated with cachexia.

2. Physiology of ghrelin

Ghrelin is a 28-amino acid hormone whose discovery was based on the ability for ghrelin to bind to the GHSR-1a in the hypothalamus and stimulate growth hormone release (Kojima et al., 1999). Ghrelin contains a unique n-octylation of serine residue ser-3 catalyzed by ghrelin-O-acyltransferase (GOAT) prior to its secretion (Gutierrez et al., 2008; Yang et al., 2008). In acylating ghrelin, GOAT utilizes fatty acids absorbed from the diet, including C6–C10 fatty acids, with a strong preference for C8 (Nishi et al., 2005). This acetylation is essential for ghrelin's binding to the GHSR-1a (Kojima et al., 1999) but as described below, may not be necessary for all of its actions.

Ghrelin is released primarily from endocrine cells in the antrum of the stomach and levels of total ghrelin rise in response to time since last feed (Cummings et al., 2002). The regulation of ghrelin release is at least partly in response to the availability of energy dense fatty acids (Kirchner et al., 2009). As such, while ghrelin has traditionally been seen as a meal-initiating hormone, it may also have properties of alerting growth- and appetite-regulating centers in the organism regarding the availability of calorie-dense food sources.

Ghrelin's actions on energy balance are mediated in part via its effects on central appetite centers such as the central melanocortin system (Fig. 1) (DeBoer and Marks, 2006; DeBoer, 2010). Ghrelin binds to GHSR-1a in the arcuate nucleus and ventromedial nucleus. In the case of the melanocortin system, ghrelin stimulation results in an increase in expression and release of the orexigenic peptide agouti-related peptide (AgRP) and neuropeptide-Y (Chen et al., 2004) and a decrease in expression of the anorexigenic peptide pro-opiomelanocortin (POMC), which is then cleaved to α-melanocyte-stimulating peptide (α-MSH) (Cowley et al., 2003). These effects ultimately lead to a decrease in signaling at the melanocortin-4 receptor (MC4R) and an increase in signaling at the Y-1 receptor, with the result being altered signaling at second order neurons and downstream effects of increased food-seeking behavior and decreased basal metabolic rate (Marks et al., 2001; Laviano et al., 2008).

However, ghrelin's actions pertinent to cachexia are not limited to these central effects. Additional effects are as follows:

1. *Inflammation*: GHSR-1a is expressed on lymphocytes, and administration of ghrelin or GHSR-1a agonists has been shown to decrease expression of inflammatory cytokines in monocytes and T-cells (Dixit et al., 2004) and decrease systemic inflammation in rodent models of inflammation (Chang et al., 2003; Granado et al., 2005), which may decrease the severity of processes related to cachexia.
2. *Cardiovascular*: Ghrelin has cardiovascular effects, including increased cardiac output and decreased blood pressure (Nagaya et al., 2001c, 2004), as reviewed by Isgaard and Granata in this special issue. These effects are discussed further in the section on cachexia from chronic heart failure (CHF).
3. *Fat storage*: Ghrelin has potent effects on fat storage, which may provide important energy reserves for the organism as the processes of cachexia continue (Tschop et al., 2000).
4. *Gastric motility*: Ghrelin administration accelerates the rate of gastric emptying in humans even in the presence of vagotomy (Tack et al., 2005; Binn et al., 2006), as reviewed by Jeffrey et al. in this special issue.
5. *Blood sugar maintenance during fasting*: Potentially pertinent to long-standing anorexia seen in cachexia, acyl ghrelin is necessary for growth-hormone mediated maintenance of fasting glucose levels during a prolonged fast (Zhao et al., 2010) as reviewed by Ukkola in this special issue.

In addition to these effects of acyl ghrelin via GHSR-1a, desacyl ghrelin—which does not bind to the GHSR-1a—also may exert other metabolic effects. Mice over-expressing desacyl ghrelin are smaller than wild-type mice (Ariyasu et al., 2005). Desacyl ghrelin appears to increase insulin sensitivity, increase fatty acid uptake in cardiomyocytes and decrease fat mass (Zhang et al., 2008; Lear et al., 2010). Similarly, treatment with desacyl ghrelin has effects including a partially protective effect against myocardial damage in an animal model of chemically induced cardiac injury (Li et al., 2006). Desacyl ghrelin may also have an effect on suppressing food intake (Asakawa et al., 2005), though these data have been conflicting (Ariyasu et al., 2005).

As we will see, most cachexia syndromes have been shown to have elevated levels of desacyl ghrelin at baseline and it is not known whether these elevated levels of desacyl ghrelin are causative of symptoms or a physiologic response to cachexia. Most disease states resulting in cachexia also demonstrate an elevation in acyl-ghrelin that may be expected following loss of body mass. As suggested above, the expression of GHS-R in a variety of tissues provides a wide scope of potential effects of ghrelin as a treatment for cachexia. Research has thus focused on whether use of acyl-ghrelin or other GHS-R agonists may be able to overcome the catabolic processes of cachexia.

3. Cancer cachexia

Cachexia is a feature that complicates the course of multiple different malignancies. In certain kinds of cancer—particularly gastrointestinal cancers—up to 85% of patients experience cachexia, and cachexia contributes to at least 20% of cancer deaths overall (Tisdale, 2002). The weight loss experienced by patients can be severe, including loss of up to 75% of muscle mass (Fearon, 1992), though even subtle amounts of weight loss and anorexia are associated with a worsened prognosis, poorer response to chemotherapy and increased morbidity (Barber et al., 1999). The loss of appetite may be a particularly important sign in that one survey of patients with terminal cancer found the presence of nausea or emesis was associated with a 68% decrease in survival and contributed to a substantial decrease in quality of life (Vigano et al., 2004).

As is true of most diseases associated with cachexia, the presence of underlying inflammation has been implicated as exhibiting important contributions in the production of cancer cachexia and may be an important target of ghrelin's actions in this setting. Pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α can be produced by tumor cells, as well as from the host response to tumor (Deans and Wigmore, 2005). Up to 50% of cancer patients exhibit evidence of elevated inflammation at diagnosis (Falconer et al., 1995) and the associated increase in cytokines is strongly implicated in producing anorexia, at least partly due to action at the central melanocortin system (Marks et al., 2001), as discussed in the previous section (Fig. 1).

In the setting of malignancy, serum levels of acyl and desacyl ghrelin are already elevated 25–50% above normal among individuals bearing a variety of cancers, including those due to lung, breast, colon and prostate cancers (Shimizu et al., 2003; Garcia et al., 2005; Malendowicz et al., 2009). The cause of these higher levels may be multi-factorial, as each of these types of cancer and several others have been reported to express ghrelin (Nikolopoulos et al., 2010). Nevertheless, the elevation in ghrelin in cancer cachexia is likely