REVIEW

Ghrelin for cachexia

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Abstract Ghrelin, a natural ligand for the growth hormone (GH)-secretagogue receptor, is primarily produced in the stomach. Administration of ghrelin stimulates food intake and GH secretion in both animals and humans. Ghrelin is the only circulating hormone known to stimulate appetite in humans. As GH is an anabolic hormone, protein stores are spared at the expense of fat during conditions of caloric restriction. Ghrelin also inhibits the production of anorectic proinflammatory cytokines. Thus, ghrelin exhibits anti-cachectic actions via both GH-dependent and -independent mechanisms. Several studies are evaluating the efficacy of ghrelin in the treatment of cachexia caused by a variety of diseases, including congestive heart failure, chronic obstructive pulmonary disease, cancer, and end-stage renal disease. These studies will hopefully lead to the development of novel clinical applications for ghrelin in the future. These studies have also facilitated a better understanding of the molecular basis of the anti-catabolic effects of ghrelin. This review summarizes the recent advances in this area of research.

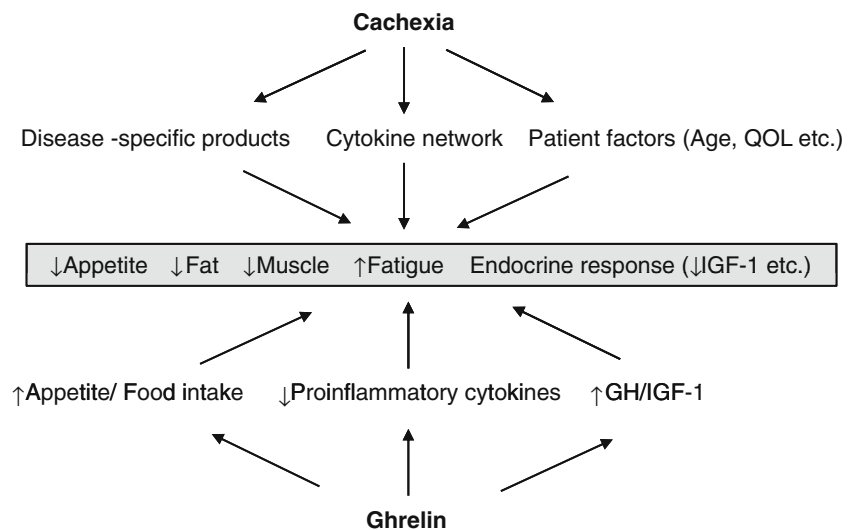**Keywords** Anorexia · Sarcopenia · Catabolism · Anabolism · Growth hormone · GHS

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1 Introduction

Ghrelin is a natural ligand for the growth hormone (GH)-secretagogue receptor (GHS-R), which possesses a unique fatty acid modification, an *n*-octanoylation, at Ser 3 [1]. Of the two circulating forms of ghrelin, acylated and unacylated (des-acyl), the acylated form is essential for the biological activity of ghrelin acting via the GHS-R. Ghrelin plays a critical role in a variety of physiological processes, including the stimulation of GH secretion and regulation of energy homeostasis by stimulating food intake and promoting adiposity via a GH-independent mechanism [2–4]. GH, which regulates insulin-like growth factor (IGF)-I levels, is an anabolic hormone that spares protein stores at the expense of fat utilization during conditions of caloric restriction. GH and IGF-1 are the major mediators of metabolism involved in the regulation of energy balance. Ghrelin inhibits the production of anorectic proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α [5, 6]. The combination of these actions suggests this peptide has benefits for the treatment of cachexia (Fig. 1).

Cachexia is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass [7]. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance, and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption, and hyperthyroidism and is associated with increased morbidity. Recently, several trials attempting to treat cachexia of different etiologies with ghrelin have been expanded. This review summarizes the recent advances in this area of research.

Fig. 1 Mechanisms of cachexia and the therapeutic benefits of ghrelin. *QOL* quality of life

2 Physiologic and pharmacologic actions of ghrelin

2.1 Orexigenic action

Ghrelin has a well-established role in stimulating appetite and increasing food intake [8, 9]; peripheral administration of ghrelin stimulates GH secretion and food intake in both animals and humans [10, 11]. Ghrelin is the only hormone known to stimulate appetite after peripheral administration. Ghrelin, which increases c-fos expression in the arcuate nucleus, also activates hypothalamic neuropeptide Y/Y1 receptors and agouti-related peptide pathways [12–14]. In addition, ghrelin induces food intake via the orexin pathway [15]. These functions are mediated at least in part by vagal nerve pathways [16]. Repeated administration of ghrelin resulted in significant weight gain in rats [17] and patients with chronic obstructive pulmonary disease (COPD) [18]. Increases in adiposity were associated with body weight gain in animal experiments [17, 19, 20], while adiposity decreased in humans [21–23]. This discrepancy may result from the differences in the doses and frequencies of ghrelin administration. Long-term, twice-weekly injection with low-dose ghrelin (40 μg/kg) significantly decreased fat mass in aged mice [24]. While weekly food intake did not increase under these conditions, ghrelin-induced GH secretion may have contributed to low adiposity. In contrast, lean body mass increased in rodents [24, 25] and humans [18, 21–23] following ghrelin administration. Also, lean body mass increases following ghrelin mimetic administration [26, 27]. These effects, which reflect increases in muscle mass, are promising for cachexia treatment, as losses in body weight and sarcopenia are characteristic features of cachexia.

2.2 Stimulation of GH secretion

Ghrelin strongly stimulates GH secretion in humans [28–31], severalfold more potently than GHRH under similar circumstances. Furthermore, ghrelin and GHRH synergistically increases GH release [30]. Ghrelin might also play a role on GH release in a non-acute setting [32]. GH regulates IGF-I levels, promotes anabolism, and increases muscle strength [33, 34]. While GH enhances lipolysis, IGF-1 stimulates protein synthesis, myoblast differentiation, and muscle growth. Recombinant GH is currently approved by the U.S. Food and Drug Administration for use in HIV/AIDS wasting, parenteral nutrition-dependent short bowel syndrome, pediatric chronic kidney disease, and adult and pediatric GH-deficiency states [35]. Pharmacological doses of this agent, however, cause problematic side effects, such as dose-related arthralgias, carpal-tunnel syndrome, paresthesias, insulin resistance, sodium retention, and peripheral edema. In contrast, stimulation of GH production to supraphysiological levels following ghrelin administration has a paucity of side effects.

Ghrelin's ability to increase circulating IGF-1 levels has been demonstrated in human studies of congestive heart failure (CHF) and COPD, in which 3-week ghrelin injections tended to increase IGF-1 levels [18, 36]. This effect is less evident as that seen for growth hormone secretagogues (GHS), such as MK-677 and anamorelin (RC-1291). Long-term treatment (6 months) with MK-677 in patients with hip fractures increased IGF-1 levels by 84% in comparison to 17% after placebo [37]. Anamorelin treatment induced impressive increases in food intake in a 12-week trial of cancer cachexia; post-treatment IGF-1 levels were 36.5 ng/mL after anamorelin treatment in comparison to 5.95 ng/mL after placebo. In a 6-day trial

of healthy volunteers, post-treatment IGF-1 levels increased to greater than 60 ng/mL after anamorelin treatment in comparison to <0 ng/mL after placebo [38, 39]. In our study of patients undergoing total hip replacement for osteoarthritis, serum IGF levels changed significantly following eight daily ghrelin injections; the changes in post-treatment IGF-1 levels were 30.0 ng/mL for ghrelin in comparison to 5.6 ng/mL for placebo. These changes were not observed after 21 daily treatments. In males, however, serum IGF-1 levels after ghrelin treatment remained elevated in comparison to the placebo group. Thus, the timing and duration of ghrelin injection and the subjects receiving treatment (e.g., disease features and sex) may influence the effect of ghrelin on IGF-1 levels. In addition, serum levels of IGF-1, which is primarily produced by the liver, reflect the systemic effects of IGF-1. GH also induces the synthesis of IGF-I in non-hepatic tissues. The local (autocrine/paracrine) effects of IGF-1 may play distinct roles in various tissues, including muscle mass regulation [34, 40]. For instance, local muscle-restricted IGF-1 transgene expression accelerates the regeneration of injured skeletal muscle in mice, modulating inflammatory responses and limiting fibrosis [41].

2.3 Anti-inflammatory action

Evidence that ghrelin exerts anti-inflammatory actions has been accumulating. Ghrelin suppresses the production of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α both in vitro [5, 42] and in vivo [43–45]. In clinical trials, daily administration of ghrelin for 3 weeks decreased inflammatory cytokine levels and neutrophil density in sputum from patients with chronic respiratory infections [46]. In contrast, ghrelin induces the anti-inflammatory cytokine IL-10 [43, 47].

Ghrelin inhibits the activation of nuclear factor-κB (NF-κB), a transcription factor known to control the production of multiple proinflammatory cytokines during inflammatory insults [42, 44, 47]. Although the molecular mechanisms and cellular targets mediating ghrelin inhibition of NF-κB activation remain to be determined, the vagus nerve may play an important role in the ghrelin-mediated inhibition of proinflammatory cytokine release [44, 48]. Cachexia and muscular wasting occur via protein degradation by the ubiquitin–proteasome pathway [49]. Two muscle-specific ubiquitin ligases, muscle RING-finger protein-1 (MuRF1) and atrogin-1/muscle atrophy F-box (MAFbx), are upregulated under catabolic conditions. NF-κB activation may regulate skeletal muscle proteasome expression and protein degradation. The elevations in MuRF1 and MAFbx expression seen in skeletal muscle after thermal injury, arthritis, and dexamethasone administration were normalized, attenuated, and prevented, respectively, by

ghrelin or GHS administration [50–52]. IGF-1 prevents the expression of MuRF1 and MAFbx by inhibiting Forkhead box O transcription factors via stimulation of the phosphatidylinositol-3-kinase (PI3K)/Akt pathway. The IGF-1 receptor triggers activation of several intracellular kinases, including PI3K [53]. Thus, the effects of ghrelin on NF-κB activation and IGF-1 synthesis are favorable for minimizing inflammatory responses and sarcopenia in patients with cachexia.

2.4 Other actions

The role of ghrelin in stimulating gastric emptying and acid secretion is well-established [54]. This effect may ameliorate gastrointestinal symptoms in patients with anorexia–cachexia syndrome. Ghrelin also increases endogenous nitric oxide release [55, 56], which may influence the orexigenic and anti-inflammatory actions of ghrelin [57, 58]. These qualities may be important in the treatment of cachexia.

3 Plasma ghrelin levels in cachexia

Plasma ghrelin levels are elevated in cachectic conditions caused by a variety of underlying disorders [59–63]. Although this phenomenon has been called "ghrelin resistance," these elevations may be a compensatory response reflecting the negative energy balance state. While there is usually an inverse relationship between plasma ghrelin levels and body mass index (BMI), no significant difference in ghrelin levels between normal subjects and cachectic patients after matching for BMI. In patients with end-stage renal disease (ESRD), conflicting results (i.e., increases [64–66], decreases [67], or no change [67, 68]) for circulating ghrelin concentrations have been reported [69]. Aygen et al. recently reported elevations in both ghrelin and des-acyl ghrelin in ESRD patients undergoing hemodialysis in comparison to age-matched healthy controls [65]. Iglesias et al. indicated that patients undergoing hemodialysis possessed similar ghrelin concentrations to the control group; only peritoneal dialysis patients exhibited significantly lower ghrelin concentrations at baseline than those found in patients on conservative management [67]. These conflicting results are due, at least in part, to cross-sectional studies using different ghrelin assays that compared patients with different residual renal functions, ages, genders, and nutritional status. Residual renal function may affect the metabolism and clearance of ghrelin. Longitudinal studies following patients with renal disease using ghrelin assays measuring both ghrelin and des-ghrelin are required to determine the pathophysiologic role of ghrelin in cachexia associated with ESRD. Post-hemodialysis serum ghrelin levels are significantly lower than pre-

hemodialysis ghrelin levels, supporting the view that ghrelin is cleared by hemodialysis [65, 69, 70].

4 Clinical studies

Trials seeking to apply the effects of ghrelin to the treatment of cachexia have been expanding. These studies have sought to evaluate ghrelin as a treatment for patients with the cachexia associated with CHF, COPD, cancer, ERSD, etc. Cachexia, which manifests as excessive weight loss in the setting of an underlying chronic disease [71], is typically associated with anorexia as a major cause of weight loss. Weight loss and decreased appetite are the major causes of morbidity and mortality in patients with anorexia–cachexia syndrome. There is an immediate need for effective, well-tolerated treatments to stimulate appetite [72], prompting several trials to explore the application of ghrelin as a treatment for patients with cachexia.

4.1 CHF cachexia

Ghrelin induces a positive energy balance state through both GH-dependent and -independent mechanisms and has protective cardiovascular effects [73]. GH treatment may be especially useful in a subgroup of patients with cardiac cachexia [74]. Ghrelin stimulates food intake, induces adiposity, regulates the central nervous system to decrease sympathetic nerve outflow, and inhibits apoptosis of cardiomyocytes and endothelial cells in a GH-independent manner. Nagaya et al. investigated the effects of ghrelin on cardiac cachexia in patients with CHF [36] (Table 1). Daily administration of ghrelin for 3 weeks increased both food intake and body weight. This study also demonstrated improvements in patient exercise capacity, muscle wasting, and left ventricular function. Ghrelin treatment also resulted in significantly decreased plasma norepinephrine levels. Although this study was neither randomized nor placebo-controlled, the eight CHF patients who did not receive ghrelin (control group) were followed to rule out any time-course effects during hospitalization. None of the afore-mentioned parameters changed in patients with CHF who did not receive ghrelin therapy. Further studies will be necessary to identify the pathways involved in this ghrelin effect and to determine the best therapeutic strategies for ghrelin use to combat the wasting process found in cardiac cachexia [74]. Clinical trials are currently attempting to reproduce these data in a double-blind, placebo-controlled fashion.

4.2 COPD cachexia

Patients with COPD often exhibit some degree of cachexia [75], which is an independent risk factor for mortality in COPD; GH treatment increases muscle mass in such patients. COPD and CHF are both associated with multiple pathophysiological disturbances, including anemia and neurohormonal activation [76]. In COPD patients, ghrelin exhibits anti-inflammatory effects. Chronic respiratory infections, characterized by neutrophil-dominant airway inflammation, lead to end-stage cachexia [77]. The cytotoxicity of accumulated neutrophils against bronchial and alveolar epithelial cells induces a deterioration of pulmonary function in COPD, resulting in excess energy expenditure and weight loss in patients. Intravenous ghrelin treatment for 3 weeks reduced both neutrophil counts in sputum samples and the volume of sputum, suggesting suppression by ghrelin of excess neutrophilic influx [46].

An open-label pilot study examined the ability of ghrelin to improve cachexia and functional capacity in patients with COPD; ghrelin was administered intravenously for 3 weeks to seven cachectic patients with COPD [18]. Repeated ghrelin administration significantly increased food intake, body weight, lean body mass, and peripheral and respiratory muscle strength. Ghrelin treatment amelio-rated the exaggerated sympathetic nerve activity, as indicated by marked decreases in plasma norepinephrine levels. In cachectic patients with COPD, treatment with ghrelin improved appetite, body composition, muscle wasting, functional capacity, and sympathetic augmenta-

Table 1 Summary of clinical studies of ghrelin/GHS for cachexia therapy

Diseases	Reference	Year	Study design	Ghrelin/GHS administration
CHF	[24]	2004	Open-label pilot study	Ghrelin, 2 μg/kg b.i.d. for 3 weeks, i.v.
COPD	[27]	2005	Open-label pilot study	Ghrelin, 2 μg/kg b.i.d. for 3 weeks, i.v.
Cancer cachexia	[76]	2004	Acute, randomized, placebo-controlled, cross-over study	Ghrelin, 5 pmol/kg/min, i.v., for >180 min
Cancer cachexia	[31]	2007	Randomized, placebo-controlled study	Anamorelin, 50 mg/day, oral, 12 weeks
Cancer cachexia	[77]	2008	Randomized, placebo-controlled, cross-over study	Ghrelin, 2 or 8 μg/kg, i.v., for 4 days, once a day
ESRD	[79]	2005	Acute, randomized, placebo-controlled, cross-over study	Ghrelin, 3.6 nmol/kg, s.c.
ESRD	[80]	2009	Randomized, placebo-controlled, cross-over study	Ghrelin, 12 μg/kg, s.c., for 1 wk, once a day

tion. Subsequently, another placebo-controlled trial demonstrated that ghrelin increased both appetite and body weight with an apparent dose-dependent trend towards improved physical performance (chair stand score) [78]. A larger clinical trial is currently being conducted to confirm these data in a double-blind, placebo-controlled fashion. Comparisons of this treatment to current standard medications will be required [76].

4.3 Cancer cachexia

Anorexia, frequently encountered in cancer patients, is one of the major causes of malnutrition and cachexia in this patient population. Ghrelin administration resulted in significant increases in weight and food intake in rodent models of cancer cachexia [79–81]. In all studies, ghrelin improved both food intake and weight gain in rodent models. DeBoer et al. determined that weight gain resulted from a reversal in the loss of lean body mass, a critical component of cachexia [81].

Several randomized, double-blind placebo-controlled trials have demonstrated the efficacy and safety of ghrelin or GHS in patients with cancer-associated cachexia [38, 82, 83]. Nearry et al. performed a randomized, placebo-controlled, cross-over clinical trial to determine if ghrelin could stimulate appetite in seven cancer patients with severe anorexia [82]. Ghrelin infusion resulted in a marked increase in energy intake in comparison to saline-treated controls; all patients in the study demonstrated increased food consumption. The meal appreciation score was also higher in ghrelin-treated individuals. Strasser et al. detailed a randomized, double-crossover, phase 1/2 study in patients with advanced cancer [83]. They infused a low or high dose of ghrelin or placebo before lunch daily for 4 days in each course. Nutritional intake or eating-related symptoms did not differ between the ghrelin- and placebo-treated groups. More patients, however, preferred ghrelin to placebo at the middle and end of study, although this finding was not dose-dependent. In contrast to the results of Neary et al., this study did not demonstrate any increases in food intake. As the patient characteristics and study designs were very different in the two studies, further investigation will be required. Garcia et al. performed a randomized, placebo-controlled trial over a 12-week period using subjects with a variety of cancer types (predominantly lung cancer). Anamorelin was infused, which produced an improvement in total body mass trending toward increased lean mass. Quality of life, however, was unchanged between the groups receiving anamorelin and placebo.

An important concern regarding the use of ghrelin in cancer cachexia is that ghrelin may increase growth factors, such as GH and IGF-1, to stimulate tumor growth. Additionally, ghrelin itself may have mitogenic potential. As far as we know, no in vivo data has examined the differences in tumor growth after ghrelin or GHS treatment. Long-term, large-scale clinical trials are required to determine if ghrelin treatment promotes tumor growth.

4.4 End-stage renal disease

ESRD is a chronic condition frequently associated with nutritional dysfunction [84]. This type of malnutrition is highly resistant to intervention and a major predictor of morbidity and mortality for patients on either peritoneal dialysis or hemodialysis. Wynne et al. sought to determine if a single injection of ghrelin could enhance food intake in patients with evidence of malnutrition receiving maintenance peritoneal dialysis [85]. Nine peritoneal dialysis patients exhibiting mild to moderate malnutrition administered either ghrelin or a saline placebo subcutaneously were examined in a randomized, double-blind, cross-over protocol. Ghrelin administration significantly increased mean absolute energy intake during the study meals and maintained nonsignificant increases observed in energy intake over the first 24 h without a subsequent rebound. This research group has subsequently sought to analyze the efficacy of repeated ghrelin administrations in malnourished dialysis patients [86]. They performed a double-blind randomized cross-over study of a week of daily subcutaneous ghrelin injections in a group of 12 malnourished dialysis patients. Ghrelin administration significantly increased appetite, with increases in energy intake noted at the first study meal. Persistence of this effect throughout the week was confirmed by food diaries and final study meals, indicating that daily ghrelin treatment achieved a sustained positive change in energy balance in malnourished dialysis patients. In support of this data, an animal study using a nephrectomized rat model of renal cachexia demonstrated that daily treatment for 2 weeks with ghrelin or two GHS agents (BIM-28125 and BIM-28131) resulted in increased food intake, improved lean body mass accrual, and decreased circulating inflammatory cytokines [25]. Long-term studies are needed to demonstrate the efficacy in improving appetite, weight gain, lean body mass, and quality of life.

4.5 Others

Ghrelin treatment has also been applied to other causes of anorexia, sarcopenia, and emaciation, including anorexia nervosa [87], functional dyspepsia [88], aging [21], post-gastrectomy anorexia [22], esophagectomy [23], chemotherapy [89, 90], and thermal injury [91]. In addition, the effects of ghrelin mimetics were examined in age-dependent sarcopenia [21, 32]. These applications certainly provide additional insight into the successful treatment of cachexia, a wasting syndrome developing in the setting of a variety of chronic illnesses.

5 Conclusion

Ghrelin exhibits anti-cachectic effects in a number of animal and human studies. Ghrelin treatment is safe and well-tolerated. Several larger-scale clinical trials are currently attempting to reproduce these effects for the treatment of cachexia, including that associated with CHF, cancer, COPD, and ESRD. Long-term, large-scale trials are eagerly awaited to determine if ghrelin is an effective therapy for cachexia.

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