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CLINICAL DEVELOPMENT OF GHRELIN AXIS DERIVED MOLECULES FOR CANCER CACHEXIA TREATMENT

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Abstract

Purpose of the Review—Cachexia is a devastating complication of cancer for which there is no approved treatment. Here we review the clinical development of ghrelin and ghrelin mimetics (also known as growth hormone [GH] secretagogues or GHS) for cancer cachexia treatment.

Recent Findings—Ghrelin, a novel hormone known to increase appetite, lean and fat mass and GH secretion is being developed as a therapeutic option for cancer anorexia/cachexia syndrome (CACS). Recent animal studies suggest that it may also decrease inflammation and that some of its effects may be independent of its only known receptor, the GHS receptor-1a (GHSR1a). Clinical studies recently have shown that administration of ghrelin or GHS improves appetite and quality of life as assessed by questionnaires. Weight gain, increased food intake and better tolerance to chemotherapy have also been reported. This treatment appears to be safe and well-tolerated.

Summary—Ghrelin and GHS have the potential to effectively prevent or reverse CACS. Preliminary studies show improvements in weight stabilization and appetite with short-term usage. Further studies are required to fully characterize the role of ghrelin and GHS for the treatment of CACS and to establish the safety of this approach.

Keywords

cachexia; ghrelin; ghrelin mimetics; GH; cancer

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Introduction

In 1981, a number of peptides were shown to induce growth hormone secretion through an unknown mechanism and were called growth hormone secretagogues (GHS) (1). Clinical development of these compounds started for several indications including frailty of aging and osteoporosis in spite of their mechanism of action being unknown. In 1996, the receptor for these GHS was identified and named GHS receptor 1a (GHSR1a) with its presence being detected primarily in the pituitary gland and hypothalamus (2) but also in other brain regions and in a wide range of peripheral tissues, including stomach, intestine, pancreas, spleen, and others. Notably this receptor is not present in liver, adipose tissue or skeletal muscle (3). It was only in 1999 that the endogenous ligand for the receptor was identified by Kojima et al (4) and it was named “ghrelin”. Ghrelin is primarily secreted from the stomach cells but it is also made in other tissues including lung, pancreas, liver, adipose tissue and muscle (5). Besides inducing an acute release of GH from the pituitary, ghrelin has other important biological functions in both humans and animals including a central role in appetite and energy balance regulation and modulation of fat and muscle mass (6). Although ghrelin binds to the GHSR1a and signals through this receptor to exert many of its endocrine effects, including the release of GH, it is now clear that there is an alternative ghrelin receptor. Ghrelin has a number of actions in cell types that do not express the GHSR1a, and these effects must be mediated through the hypothesized alternative receptor (7, 8).

The cancer anorexia-cachexia syndrome (CACS) is a common complication of cancer and other chronic conditions and contributes to a decrease in functional performance in these populations. It usually takes a heavy toll on patients' quality of life and is associated with poor survival. Despite the importance of these symptoms, treatments are lacking (9). Given ghrelin's action profile, there is considerable interest in ghrelin as a modality to be utilized for treatment of catabolic states such as cachexia. In this review we examine the role of ghrelin in energy homeostasis and metabolism, the mechanisms by which it counteracts weight loss and present trial experience with ghrelin or GHS (now also referred to as ghrelin analogues, ghrelin receptor agonists or ghrelin mimetics) in the setting of cancer cachexia.

Mechanisms of Action of Ghrelin and GHS

Ghrelin affects multiple pathways that are key to the regulation of body weight, body composition, and appetite in the setting of cachexia (Figure 1). Ghrelin stimulates food intake and increases body weight in rodents (10), and it also increases food intake in both lean and obese humans (11, 12). Ghrelin and GHS administration stimulate food intake within 1h of administration and continuous administration results in sustained feeding (13). This effect is mediated through the GHSR1a receptor present in neurons located in the arcuate nucleus of the hypothalamus and it is seen whether ghrelin is administered centrally or peripherally (14). Animal studies also suggest that ghrelin facilitates hedonic eating (15) but human data to confirm this observation is lacking. Ghrelin also plays a role in enhancing GI motility especially in the proximal gut and this may contribute to a decrease in nausea and vomiting that are frequent complications of cancer and its treatments (16). Ghrelin can also affect energy balance by decreasing energy expenditure via suppressing sympathetic nerve system output to brown adipose tissue (BAT), thereby decreasing thermogenesis (17).

Taken together, the stimulatory and inhibitory effects of ghrelin on energy intake and expenditure, respectively, lead to a positive energy balance and weight gain. This combination of effects may be particularly important in the setting of cancer cachexia where appetite is usually decreased and energy expenditure usually increased (18, 19).

Inflammation may play a central pathogenic role in the decreased food intake and increased energy expenditure seen in most chronic conditions associated with the anorexia and cachexia syndrome (20). It has also been suggested that activation of inflammatory pathways can induce muscle wasting and increased lipolysis in adipose tissue by acting directly in these tissues (21, 22). Ghrelin has anti-inflammatory properties decreasing tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, and interferon (IFN)- γ in an animal model of sepsis (23). In other studies, exogenously administered ghrelin suppressed cytokines regardless of the model used (24). Increased cytokines in the hypothalamus results in activation of anorexigenic pathways and a subsequent decrease in food intake and ghrelin may inhibit this inflammatory process centrally suggesting that ghrelin's anti-inflammatory effects contribute to its orexigenic effects in the setting of cachexia.

Ghrelin also favors adiposity through activation of lipogenic pathways in the central nervous system independently of its orexigenic effects (25). It also decreases adipose tissue lipolysis and lipid oxidation induced by cisplatin and by anorexia (26) in animal models with the net result of preserving fat mass. Tumor models have also shown that ghrelin or GHS administration preserves fat mass in this setting (27).

The GH/IGF-1 axis is one of the primary anabolic pathways in skeletal muscle (28). Studies have shown that both GH and IGF-1 treatments increased body weight primarily through an increase in lean body mass (LBM) (29, 30). GH increases the expression of IGF-1 in rodent muscle leading to growth, and exogenous IGF-1 increases skeletal muscle protein synthesis in mice and humans. Ghrelin and GHS are powerful stimulants for the release of growth hormone (4, 31), and this leads to an increase in the hepatic production of insulin-like growth factor-1 (IGF-1). These increases in IGF-1 are associated with a decrease in proteolysis and increased protein synthesis, suggesting that this mechanism may contribute to the preservation of muscle mass induced by ghrelin. Given that anorexia is known to induce muscle atrophy, it is also likely that the orexigenic effects of ghrelin indirectly contribute to muscle mass preservation. Recent data also suggest that ghrelin increases muscle protein synthesis and decreases proteolysis through other mechanisms that are independent of its effects on food intake, GH secretion and that are not mediated through the GHSR1a (7).

In summary, ghrelin has the potential to positively affect appetite, energy expenditure, inflammation, adipose tissue and muscle and ultimately prevent or ameliorate cachexia. This is particularly appealing in the setting of CACS where multiple mechanisms are involved in its pathogenesis.

Experience with Ghrelin or GHS in Healthy Subjects

Early work by Wren et al. demonstrated that healthy volunteers consumed more calories with an increased energy intake of $28 \pm 4\%$ after 180 minutes of ghrelin infusion compared to

placebo (11). Druce et al. replicated these findings in their cohort of 8 men and 8 women with subcutaneous ghrelin administration showing an increase in food intake of 27% (12). Akamizu et al. established safety and tolerability of acute ghrelin infusion of 1 mcg/kg or 5 mcg/kg in healthy subjects and found only mild abdominal discomfort, flushing and somnolence as side effects; which were mild, transient and overall well tolerated (32). Also, ghrelin administration has been shown to decrease energy expenditure in non-cancer human and animal models (33).

Since ghrelin is a 28-aminoacid peptide with a half-life of 15 to 30 minutes, it needs to be administered parenterally. Ghrelin analogs (GHS) are stable compounds with longer half-lives that can be administered orally. The GHS MK-677 was shown to increase body weight and reverse the negative nitrogen balance induced by starvation independently of its orexigenic effects suggesting that its effects are not entirely mediated through an increase in appetite and that other mechanisms, such as a decrease in energy expenditure, are involved (34). Also, when given to healthy individuals age 60-81 years, MK-677 increased GH and IGF-1 to match those of young healthy individuals without major side effects except a mild increase in glucose and insulin resistance levels. In this study it also increased lean body mass, subcutaneous fat and body weight over a 12-month period (35). Merriam et al. randomized older adults with mild functional limitation to receive the orally active GHS capromorelin vs. placebo. Although the study was terminated early according to predetermined treatment effect criteria, capromorelin increased GH, IGF-1, body weight, lean body mass, walking speed and stair climbing power with only small increases in fasting glucose, glycosylated hemoglobin, and indices of insulin resistance (36).

Garcia et al. looked at the effects of the GHS RC-1291, now called anamorelin, in a phase I randomized double blind placebo controlled cross over study. Thirty-two healthy volunteers were randomized to receive 25mg, 50mg or 75 mg of RC-1291 vs. placebo for 5 days. The study demonstrated no major adverse events and a dose-related increase in weight of 1.25 ± 0.725 kg ($p=0.002$) in the 50 mg group and 1.16 ± 0.651 kg ($p=0.002$) in the 75 mg qd vs. placebo (37). Anamorelin also induced a dose-dependent increase in GH, IGF-1 and on its binding protein, IGF binding protein-3 (IGFBP-3) (31), and small increases in insulin resistance. This data is particularly relevant since this GHS is currently the most advanced compound in this class in development for the indication of cancer cachexia. Another GHS in development for treatment of cancer cachexia is macimorelin (formerly known as AEZS-130, ARD-07 and EP-01572). It is a novel GHS with good stability and oral bioavailability that binds the GHS-R1a receptor with similar affinity to ghrelin (38). In Phase I clinical studies in healthy volunteers, macimorelin stimulated GH release in a dose-dependent manner, achieving maximum blood levels within one hour with good tolerability (39).

Taken together, the data suggest that administration of ghrelin or GHS to healthy individuals, increases appetite and food intake acutely, and that chronic administration leads to increases in body weight primarily through an increase in lean body mass but possibly through an increase in fat mass as well. GHS administration also increases GH tone and IGF-1, which is likely to contribute but it is not the only mechanism by which these agents increase lean mass. These increases in muscle mass may be followed by increases in

function, particularly in individuals with functional limitation. These interventions appear to be well-tolerated, causing a mild increase in insulin resistance and glucose levels.

Experience with Ghrelin and GHS in Cancer Cachexia

The appetite-enhancing effects and good tolerability of ghrelin and GHS in healthy volunteers made them a potential therapeutic option in various catabolic states including CACS. Neary et al. first studied 7 patients with a variety of metastatic cancers (5 breast, one colon, one melanoma) and anorexia (excluding those that had undergone surgery, radiotherapy or that had received progestational agents or glucocorticoids in the previous month) in a randomized, blinded, placebo-controlled crossover design. Similar to healthy volunteers, they demonstrated that a ghrelin infusion of 0.5 pmol/kg/min (~3mcg/kg/hr) for 3 hours resulted in an increase in energy consumption of 31% compared to placebo. Perceived pleasantness of food also significantly increased in the ghrelin group (40). Strasser et al. randomized 21 patients with advanced incurable cancer, loss of appetite and a weight loss ≥2% over 2 months or ≥5% within 6 months before the study unrelated to surgery to receive either a low dose (2 mcg/kg) or high dose (8 mcg/kg) ghrelin infusion alternating with placebo over 1h in a randomized and blinded manner one week apart. Eighty-one % and 63% of patients preferred ghrelin infusion over placebo at day 8 and at the end of the study (41). Ghrelin was well-tolerated with no safety concerns; however, no appreciable differences in food intake or other symptoms were found. It is possible that this study might have been underpowered or that the doses used were not sufficient to elicit a response since a Swedish study that randomized 31 patients with metastatic gastrointestinal cancer, anorexia and weight loss ≥5% and not receiving treatment for their tumor at the time of recruitment to receive high dose (13 mcg/kg) vs. low dose (0.7 mcg/kg) ghrelin subcutaneously daily for 8 weeks showed more positive results. The high dose group had improved appetite scores and decreased loss of adiposity without affecting tumor progression (42). Hiura et al. randomized 42 esophageal cancer patients (with stage II-III disease and able to eat solid foods) to receive either ghrelin infusion (3mcg/kg) twice daily for 7 days with cisplatin-based neoadjuvant chemotherapy or placebo. Food intake was the primary endpoint, and was significantly higher in the ghrelin group than in the placebo group (18.2 ± 5.2 kcal/kg/day vs. 12.7 ± 3.4 kcal/kg/day [$P = 0.001$]). Appetite scores based on a visual analog scale were also significantly higher in the ghrelin group and patients in the ghrelin group reported less anorexia and nausea than patients in the control group. Significant worsening in quality of life scores, appetite, nausea and vomiting, and global health status was noted with placebo. Also, ghrelin treatment led to less toxicity from chemotherapy (as assessed by need to have dose modification) and reduced length of hospital stay from 23.5 days in control to 18.4 days in the ghrelin group (16).

GHS also have been evaluated in the setting of CACS. In a multi-centre phase II study, 16 patients with weight loss ≥5% over the previous 6 months due to a variety of incurable cancers and good performance status were treated with oral anamorelin 50 mg once daily vs. placebo for 3 days followed by a washout period of 5 to 7 days and then cross-over to the other group for 3 more days. Weight increased ~1kg with anamorelin compared to placebo. Patient-reported QOL scores were also significant favoring anamorelin. Four patients reported adverse events with the study drug which were mild. Reported events were

hyperglycemia, nausea and dizziness. Food intake was higher with anamorelin but it did not reach statistical significance (43). Table 1 summarizes the salient findings from the published studies of ghrelin or GHS use in CACS. The data consistently shows improved patient-reported appetite scores and positive impact on quality of life as assessed by questionnaires. Weight gain and increased food intake are reported by some but not all studies. It is also possible that the improvement in these symptoms may allow patients to better tolerate chemotherapy. Lastly, treatment appears to be safe and well-tolerated.

Safety of Ghrelin and GHS in the Setting of Cancer

One theoretical concern regarding use of ghrelin in cancer patients is that ghrelin may cause tumor progression via its GH/IGF-1 stimulatory effect or through other unidentified mechanism. Studies reporting cell-based experiments have given conflicting results with some showing an increase and some showing a decrease in cell proliferation with ghrelin (44, 45). However, whole-animal models and human studies where ghrelin or GHS have been used, have not shown an increase in tumor proliferation, although none of these animal models have reported survival and all human studies were not designed or adequately powered to address this question (27, 46, 47). There is a need for future larger trials with extended follow-up to determine long-term safety of these interventions.

Ongoing Clinical Trials in Cancer Cachexia

Anamorelin is undergoing phase III clinical trials in patients with stage III-IV non-small cell lung cancer planning to initiate a new chemotherapy and/or radiation therapy regimen and involuntary weight loss $\geq 5\%$ within 6 months prior to screening or a screening body mass index (BMI) $<20 \text{ kg/m}^2$ to determine the safety and efficacy of this intervention (NCT01387269, NCT01387282, NCT01395914). Lean mass by DEXA and handgrip strength are the primary endpoints of this study but its effect on quality of life (FACIT-F [Functional Assessment of Chronic Illness Therapy-Fatigue] and the FAACT [Functional Assessment of Anorexia/Cachexia Treatment]) and survival are also being assessed. Other mechanistic studies in the setting of cancer cachexia are also underway to better characterize the role of the ghrelin axis in this setting. A study involving the use anamorelin (NCT01505764) in patients with stage II-IV non-small cell lung cancer and weight loss of $\geq 5\%$ over a period of 6 months, $\geq 10\%$ body weight loss over a period of 12 months or BMI <20 with a weight loss $>2\%$ over a period of six months, is currently evaluating its effect on lean body mass (assessed by total body potassium) handgrip strength, quality of life and appetite. Another study is looking at the role of the GHS macimorelin (NCT01614990) in patient with involuntary weight loss of at least 5% over the previous 6 months, incurable cancer (solid tumors) and ECOG performance status of 0-2 on body weight, IGF-1 and quality of life scores.

Ghrelin-related compounds potentially useful for CACS

The traditional Japanese herbal medicine rikkunshito, has been recently identified to function as a ghrelin enhancer (48) that prevents weight loss, anorexia, nausea and survival associated with cancer or chemotherapy use in animal models (49, 50). Fujitsuka et al. also reported an uncontrolled clinical trial where 6 patients with advanced pancreatic cancer receiving rikkunshito had prolonged survival compared to patients not receiving it (50).

More studies are needed to confirm these findings and test the efficacy of this intervention. Splice variants of ghrelin have also been proposed for the treatment of cachexia and initial studies in animal models showed that exogenous administration of a 24-aminoacid splice variant of ghrelin, DLN101, increased food intake, GH secretion, lean and fat mass (51). No clinical studies using this or other splice variants have been published.

Conclusions

Ghrelin is an orexigenic hormone that increases energy intake and muscle mass and function, probably by a combination of mechanisms including an increase in food intake, upregulation of the GH/IGF-1 axis and other yet not well-characterized mechanisms. It also preserves fat mass by promoting lipogenesis and decreasing lipolysis. It improves the hedonic value of food, and, in animal models, it decreases markers of inflammation. Although recent evidence from pre-clinical models suggest that GHSR1a may not mediate all the effects of the ghrelin, GHS appear to have all the effects of ghrelin in human and animal models tested so far.

Activation of this pathway has the potential to offset the devastating effects of CACS plaguing advanced cancer patients. Preliminary studies with ghrelin or GHS in this setting show reliable benefits in weight stabilization and appetite improvement with short term usage. Further studies are required to definitively establish the role of ghrelin and GHS for the treatment of CACS and to establish its safety.

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KEY POINTS

- Ghrelin and GHS increase energy intake, decrease inflammation and result in increased fat and muscle mass in animal models of cachexia; therefore, they have the potential to provide a multipronged approach to counter CACS.
- Preliminary clinical studies show promising results with use of ghrelin or GHS in CACS with improvement in weight, appetite and energy intake.
- Ghrelin and GHS appear to be safe and well-tolerated in healthy controls as well as patients suffering from CACS.
- There is a need for longer term, randomized, controlled trials to establish the role of ghrelin or GHS for use in this setting.

Figure 1.

Potential mechanisms of action for ghrelin or its mimetics (GHS) in cancer cachexia.

Ghrelin and GHS increase appetite through a direct effect on the arcuate nucleus of the hypothalamus. They reduce sympathetic nervous system activity, thereby decreasing energy expenditure and facilitating fat mass preservation. Growth hormone is secreted in response to ghrelin or GHS and this causes an increase in insulin-like growth factor-1 (IGF-1) in the liver that contributes to a decrease in proteolysis and increased muscle protein synthesis. Ghrelin and GHS are also likely to increase muscle mass through direct effects on myocytes. A decrease in inflammation may also mediate the effects of ghrelin/GHS in this setting.

Width of the arrows indicates strength of the effect.

Table 1

Human studies using ghrelin or GHS in cachexia (original)

POPULATION	REGIMEN	RESULTS	REFERENCE
7 Solid tumor patients vs 7 healthy controls	IV ghrelin infusion 16.8 µg/kg/min for 3 hours once	-Energy intake was increased 31% -Pleasantness of the meal increased 23%	Neary et al 2004 (40)
21 subjects with advanced incurable cancer	IV ghrelin low dose= 2 µg/kg (n=10) or high dose=8 µg/kg (n=11) over 1 hour vs placebo for two days (7 days apart)	-Increase energy intake -Increased meal appreciation score -No effect on tumor progression - Participants preferred ghrelin over placebo at the end of the study	Strasser et al 2008 (41)
31 patients with weight loss and solid GI tumors	SC ghrelin low dose low dose=0.7 µg/kg (n=14) or high dose =13 µg/kg daily (n=17) daily for 8 weeks.	-Increased appetite scores (high dose) -Decreased whole body fat loss (high dose) -Trend for improved energy balance -No effect on tumor progression	Lundholm et al 2010 (42)
42 patients with stage II-III esophageal cancer on cisplatin neo-adjuvant chemotherapy	IV ghrelin infusion 3 µg/kg twice daily vs placebo for 1 week	-Increased food intake -Better quality of life score -Less nausea and vomiting from chemo -Less toxicity from chemotherapy -Reduced hospital stay -No difference in tumor response to chemotherapy	Hiura et al 2012 (16)
16 patients with solid organ tumors	Cross-over study of anamorelin 50 mg once daily for 3 days vs placebo.	-Increased body mass (1Kg difference) -Increased appetite - Well-tolerated	Garcia et al 2012 (43)