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REVIEW

Ghrelin and its potential in the treatment of eating/wasting disorders and cachexia

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Abstract The gastrointestinal "hunger" hormone ghrelin is the only known circulating peripheral molecule with the ability to decrease body fat utilization and to increase body weight gain. Accordingly, due to ghrelin's effects to promote food intake while decreasing energy expenditure ghrelin may offer potential as a drug for treatment of eating/wasting disorders and cachexia. Therapeutic potential of ghrelin and ghrelin analogues to promote food intake and body weight gain was recently indicated in several clinical studies. The recent discovery of the ghrelin *O*-acyltransferase as the key enzyme responsible for ghrelin acylation has further deepened our understanding of ghrelin activation, thereby paving the way for more efficient targeting of the ghrelin pathway. Here, we summarize the current knowledge pertaining to the potential of the endogenous ghrelin system as a drug target for the treatment of eating/wasting disorders and cachexia.

Keywords Anorexia · Cachexia · Wasting · Ghrelin

1 Introduction

Cachexia (Greek: kakós—bad; hexis—condition) is a multifactorial syndrome characterized by substantial loss of body weight due to an involuntarily wasting of skeletal muscle and adipose tissue mass as a result of an imbalance between catabolic and anabolic processes (Fig. 1) [1, 2]. Cachexia frequently develops in advanced stages of various chronic diseases such as chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), sepsis, acquired immune deficiency syndrome and various kinds of cancer [1, 3]. Dependent on the type of tumor, cancer-cachexia is observed in 30–80% of cancer patients with patients suffering from pancreatic or gastric cancer having the highest frequency of weight loss while patients with breast cancer, non-lymphocytic leukemia, and sarcomas having the lowest [4]. Irrespective of the underlying disease, however, cachexia is associated with a low response to drug treatment, a poor quality of life, a poor prognosis, and an increased mortality rate compared to non-cachexia patients [1, 5]. Accordingly, cachexia is believed to be the immediate cause of 10–20% of all deaths in cancer patients [5].

Cachexia is frequently, but not necessarily, accompanied by anorexia, defined as the loss of the desire to eat [4, 6]. Decreased energy intake due to anorexia contributes to increased weight loss but, however, cannot solely explain the typical metabolic changes associated with cachexia, such as an excess release of pro-inflammatory cytokines and an increased activity of the sympathetic nervous system [1, 3, 4].

Cachexia is typically associated with an increased release of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNFα), Interleukin-1ß (IL-1ß), IL-6, and IL-8 [5]. Pro-inflammatory cytokines, especially TNFα and IL6, act as catabolic factors in the pathogenesis of cachexia by stimulating proteolytic pathways leading to muscle atrophy and increased adipose tissue breakdown (Fig. 1) [5]. In particular, TNFα stimulates muscle protein breakdown, causes contractile dysfunction and inhibits myogenesis and myogenic differentiation through activation of the nuclear factor-kappa B pathway [5, 7, 8]. TNFα

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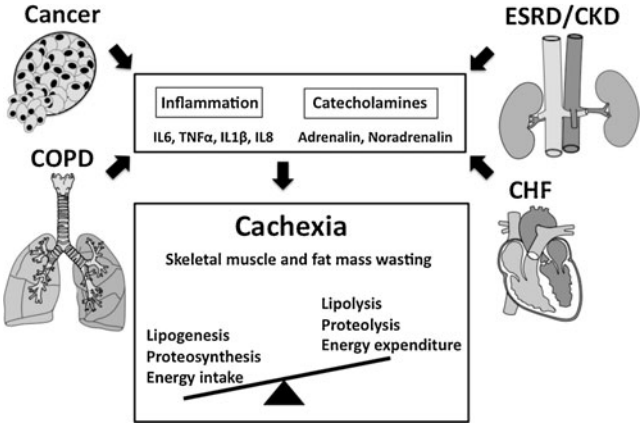

Fig. 1 Molecular mechanisms of cachexia. Typical metabolic changes associated with the development of cachexia are an increased release of pro-inflammatory cytokines as well as an overactivity of the sympathetic nervous system, as indicated by increased plasma concentrations of catecholamines. Both, pro-inflammatory cytokines and catecholamines promote catabolic processes leading to skeletal muscle and fat mass wasting, such as stimulation of lipid utilization and skeletal muscle protein breakdown while decreasing energy intake and increasing energy expenditure. *ESRD* end-stage renal disease, *CKD* chronic kidney disease, *CHF* chronic heart failure, *COPD* chronic obstructive pulmonary disease, *IL6* Interleukin 6, *IL8* Interleukin 8, *IL1β* Interleukin 1 beta, *TNFα* tumor necrosis factor alpha

further promotes wasting of adipose tissue through stimulation of lipolysis, inhibition of adipocyte differentiation and by increasing apoptosis in adipocytes [3, 5, 9].

Increased activity of the sympathetic nervous system is frequently described in patients with cachexia [4, 10, 11]. In particular, increased plasma concentrations of catecholamines as a result of sympathetic overactivity contribute to body weight loss and tissue wasting by increasing energy expenditure, stimulation of lipolysis, and stimulation of apoptosis in skeletal muscle [3, 12].

Various previous studies have, with only limited success, focused on the evaluation of potential drug targets for the treatment of eating/wasting disorders and cachexia. One of the endogenous peptides that, due to its beneficial effects on e.g. food intake, energy expenditure, and inflammation has recently reached scientific interest is the gastrointestinal "hunger" hormone ghrelin. The ability of ghrelin and ghrelin analogues to promote food intake and body weight gain in patients with eating disorders and cachexia was recently demonstrated in several clinical studies. The importance of the ghrelin system in the neuroendocrine control of energy balance has recently been highlighted in several excellent review articles [13, 14]. The aim of this review is to summarize the current knowledge pertaining to the endogenous ghrelin system as a potential target for the treatment of pathological reduced body mass, the key clinical feature of cachexia.

1.1 Ghrelin synthesis and activation

The gastrointestinal peptide hormone ghrelin was discovered in 1999 as an endogenous ligand for the growth hormone secretagogue 1a receptor (GHS-R1a) [15]. Ghrelin is synthesized as a 117 amino acid pre-prohormone, which is post-translational cleaved into a 28 amino acid peptide [16]. Ghrelin is predominantly synthesized and secreted by X/A-like cells in the oxyntic glands of the mucosa of the gastric fundus [17]. However, lower levels of ghrelin expression can also be found in, e.g., the intestine, pancreas, kidney, lung, ovaries and the brain [14]. Since its discovery in 1999, a tremendous amount of research efforts have focused on revealing ghrelin's mechanisms of action. To promote its biological action, ghrelin is acylated on its serine 3 residue by the recently discovered membrane-bound *O*-acyltransferase 4 (MBOAT4), which was later accordingly renamed to ghrelin *O*-acyl-transferase (GOAT; Fig. 2) [18, 19]. The observation that acyl-ghrelin is absent in mice lacking *Goat* indicates that Goat is the only enzyme capable to activate ghrelin in vivo [18].

1.2 Ghrelin-mediated regulation food intake and energy balance

Ghrelin is secreted from the stomach into the bloodstream under conditions of fasting, thus serving as a "hunger" hormone that signals the gastrointestinal fuel status from the periphery to the central nervous system in order to stimulate food intake and to adjust energy balance through a decrease in energy expenditure. Plasma levels of ghrelin typically follow a circadian rhythm with a preprandial rise which peaks directly at meal initiation followed by a postprandial decrease to baseline levels within the first hour after a meal [20–22]. In accordance to its role as a meal initiation hormone, ghrelin stimulates food intake and adiposity through stimulation of hypothalamic orexigenic neuropeptides [23]. In the arcuate nucleus (ARC), a hypothalamic key center in the control of energy metabolism, GHS-R1a is co-expressed with the agouti-related peptide (AgRP) and the neuropeptide Y (NPY), both prototypic anabolic neuropeptides that promote a positive energy balance through stimulation of food intake and by decreasing energy expenditure [23–25]. Accordingly, ghrelin-mediated activation of hypothalamic GHS-R1a entails an increased expression and release of NPY and AgRP in the ARC, thus entailing an activation of anabolic downstream pathways that lead to a stimulation of food intake and a decrease of energy expenditure [26–28]. Recent evidence further indicates that the ability of GOAT-mediated ghrelin acylation depends on specific dietary medium chain triglycerides as acylation sustrates [29]. These findings indicate that ghrelin, in contrast to its

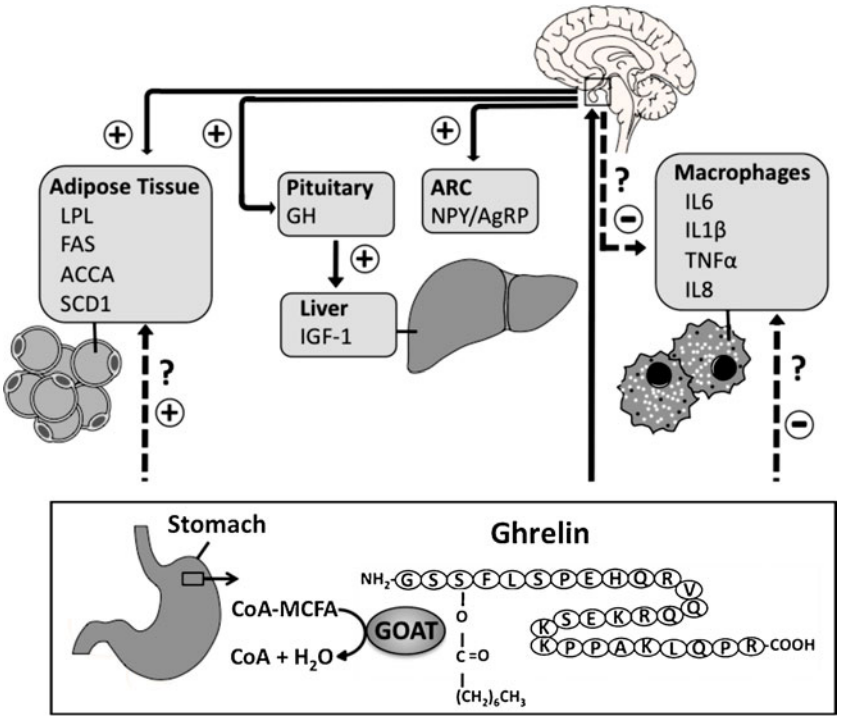

Fig. 2 Ghrelin-mediated neuroendocrine alterations of energy metabolism. Ghrelin is secreted from the stomach and is acylated at its serine 3 residues by the ghrelin *O*-acyltransferase (*GOAT*). Central-mediated effects of ghrelin include (besides others) the stimulation of food intake and the decrease of energy expenditure through stimulation of hypothalamic neurons expressing neuropeptide Y (*NPY*) and agouti-related peptide (*AgRP*). In the anterior pituitary ghrelin stimulates the release of growth hormone (*GH*), which in turn stimulates the release of hepatic insulin-like growth factor-1 (*IGF-1*). Both, GH and IGF-1 increase lean body mass by inhibition of skeletal muscle protein breakdown. In adipose tissue, ghrelin stimulates the expression of genes coding for fat-storage promoting enzymes, such as lipoprotein lipase (*LPL*), fatty acid synthase (*FAS*), acetyl-CoA carboxylase α, and steaoryl-CoA desaturase-1 (*SCD1*). Either through central or peripheral mechanisms ghrelin further inhibits the release of pro-inflammatory cytokines, such as Interleukin (IL) 6, IL 8, IL1β and the tumor necrosis factor α. *Dashed lines* indicate potential signal pathways. *ARC* arcuate nucleus

commonly accepted role as a hunger hormone, might rather serve as a nutrient sensor that signals the gastrointestinal nutrient availability to the central nervous system.

Ghrelin further stimulates the expression and release of growth hormone (GH) from the anterior pituitary gland and thus indirectly triggers expression and secretion of hepatic insulin-like growth factor-1 (IGF-1) [15, 30, 31]. Both, GH and IGF-1 are anabolic hormones known to increase lean body mass by stimulation of skeletal muscle growth and inhibition of skeletal muscle protein breakdown [32–34]. During catabolic states, such as cachexia, GH further stimulates lipolysis through increased release and oxidation of free fatty acids which leads to decreased glucose and protein oxidation and preservation of lean body mass [33]. The fundamental importance of the endogenous GOAT/ghrelin system was very recently demonstrated by Zhao and colleagues, who showed in $Goat^{-/-}$ mice that ghrelin-mediated regulation of GH release prevents death by preserving blood glucose levels under conditions of severe caloric restriction [35]. Other beneficial effects of ghrelin include a decrease of body fat utilization [36] and a decrease of sympathetic nerve activity [37–39]. In white adipocytes, ghrelin further stimulates the expression of fat-storage promoting enzymes, such as lipoprotein lipase, acetyl-CoA carboxylase α, fatty acid synthase, and steaoryl-CoA desaturase-1 [40]. In brown adipocytes, ghrelin dose-dependently lowers the expression of the thermogenesis-related mitochondrial uncoupling proteins 1 and 3, presumably through ghrelin's ability to decrease sympathetic nerve activity [40]. Ghrelin further has been reported to attenuate skeletal muscle and adipose tissue wasting by decreasing the release of pro-inflammatory cytokines, such as TNFα, IL-1ß, IL-6 and IL-8 [39–43] while increasing the release of anti-inflammatory cytokines, such as IL-10 [43]. In summary, these data indicate that the endogenous GOAT/ghrelin system plays a fundamental role in the neuroendocrine adaptation to starvation and that modulation of the ghrelin system might be an interesting target for the treatment of pathological reduced body weight and tissue wasting.

2 Ghrelin levels in patients with eating disorders and cachexia

2.1 Anorexia nervosa

Anorexia nervosa (AN) is an eating disorder of unknown etiology, typically characterized by an abnormal eating behavior with disturbances of attitudes towards body weight and shape [44, 45].

Several forms of ghrelin (octanoyl-, desacyl, (non-octanoyl) acyl-ghrelin) can be found in circulation. However, for most available immunoassays it is either not well known or not sufficiently disclosed which of those ghrelin analogues they are binding and to which extent they are cross reacting with other related peptides such as motilin. Most assays reported in the literature likely measure total ghrelin-like immunoreactivity including large amounts of presumably inactive ghrelin peptide. Nevertheless, several studies have shown a negative correlation between the body mass index (BMI) and plasma levels of ghrelin in AN [46–48]. Accordingly, plasma levels of ghrelin are elevated in the acute phase of AN [48–52] and decline to normal values upon weight restoration [49, 53, 54]. Compared to normal weight healthy controls, also plasma levels of acyl-ghrelin are elevated in patients with AN, even during all phases of an oral glucose tolerance test [46, 48]. Some studies further report higher plasma levels of acyl-ghrelin when compared to BMI-matched lean women [47, 51–56] thus indicating that impaired ghrelin sensitivity due to persistent hyperghrelinemia might play a role in the pathogenesis of AN, comparable to leptin resistance in persistently hyperleptinemic obese individuals. Persistent hyperghrelinemia might further contribute to the frequently described impairment of the GH/IGF-1 axis in AN, as plasma levels of GH are typically elevated while IGF-1 levels are paradoxically decreased in patients with AN [57–60].

The orexigenic effects of ghrelin and ghrelin analogues have been assessed in several human studies revealing that ghrelin promotes food intake in both healthy individuals [61–63] and patients with AN [64]. Ghrelin treatment of anorectic individuals for 14 days (3 μg/kg twice daily) increased energy intake by 12–36% compared to baseline values in one study [64], although in another study, where ghrelin was continuously infused for 300 min at rates of 5 pmol/kg/min, ghrelin failed to detect an effect on appetite, as assessed by a visual analog scale [65]. Potential pitfalls of these studies are, however, the limited amount of study samples and the short duration of ghrelin treatment. Notably, however, both studies report no adverse side effects of ghrelin treatment [64, 65]. A further beneficial effect of ghrelin treatment in AN include an increase of blood glucose levels [66] which is in accordance with recent findings indicating that ghrelin prevents death by preservation of normoglycemia in *Goat*$^{-/-}$ mice under conditions of starvation [35].

3 Cancer-cachexia

Several animal studies have recently assessed the potential of ghrelin in the treatment of cancer-cachexia [67–70]. Plasma concentrations of ghrelin rise with the progression of cachexia in mice inoculated with human melanoma cells [68] and ghrelin treatment of these mice attenuates cachexia by stimulation of food intake and suppression of body weight loss [67]. Similar improvements on food intake and body weight gain were reported in tumor-implanted rats treated with either ghrelin or the ghrelin analog BIM-28131 [70]. In the latter study, ghrelin increased the hypothalamic expression of *AgRP* and *NPY* whereas, interestingly, plasma levels of GH were unchanged [70]. However, not all studies were able to replicate this finding [68]. It is further noteworthy that no differences in tumor size have been observed between ghrelin and saline treated animals [67, 70].

In accordance to the animal studies, plasma concentrations of ghrelin are elevated in patients with cancer-cachexia when compared to those without cachexia [71, 72]. Continuous infusion of ghrelin (5 pmol/kg/min for 180 min) in patients with breast and colon cancer increased energy intake by 31% compared to saline treated controls [73]. However, in a 2-week randomized, double blind, placebo-controlled trial, where ghrelin was given intravenously at two time points at doses of 2 or 8 μg/kg, ghrelin failed to affect nutritional intake despite elevated plasma levels of GH indicated an increased ghrelin activity [74]. Notably, however, both studies report no adverse side effects of ghrelin treatment [73, 74].

Noteworthy is that not all studies report elevated levels of ghrelin in patients with advanced cancer and weight loss. In one study, where ghrelin was measured in 30 patients with different malignancies and 27 healthy controls, ghrelin levels were reported to be lower in patients with advanced cancer as compared to the healthy controls [75]. Further studies in other study samples are required to clarify this observation but the reduction of ghrelin levels might be attributed to the severity and progression of the disease.

Even though substantial evidence indicates the safety and tolerability of ghrelin at doses up to 10 μg/kg [62, 73, 74, 76], no long-term studies are available pertaining to the potential implication of the ghrelin/GH/IGF-1 axis on tumor growth and carcinogenesis. Both, ghrelin and/or the ghrelin receptor are expressed in various tumorous tissues, especially in tumors of the gastrointestinal tract, such as in gastric endocrine tumors [77, 78], intestinal endocrine tumors [77, 78], pancreatic endocrine tumors [79, 80] but

also in, e.g., pituitary tumors [81, 82], bronchial endocrine tumors [83] and testicular tumors [84]. It remains unknown as and to what extend ghrelin secretion from these tumors affects tumor growth and/or energy balance. Increased ghrelin secretion from tumorous tissues might be implicated in either promoting or inhibiting tumor growth via autocrine/paracrine pathways [13]. On the other hand, ghrelin released from tumors might counteract skeletal muscle and fat mass wasting by stimulation of food intake and activation of anabolic pathways. Tumor-related alterations of ghrelin secretion might thus contribute to the different rates of weight loss, which are typically observed in different kinds of cancers.

4 Chronic obstructive pulmonary disease

Cachexia is frequently described in patients with advanced stages of COPD [11, 85–87] and is considered as an independent risk factor for mortality in these patients [87, 88]. Plasma levels of ghrelin are negatively correlated with BMI in COPD patients [89] and 3-week treatment of COPD patients with ghrelin (2 μg/kg twice a day) significantly increased food intake, body weight, lean body mass, and muscle strength [11]. Intriguingly, ghrelin further increased plasma levels of GH while epinephrine levels are decreased, thus indicating a decrease of sympathetic nerve activity due to ghrelin treatment [11]. Ghrelin-mediated modulation of the GH/IGF-1 axis might be important for pulmonary cachexia as GH treatment has previously been shown to increase muscle mass in patients with COPD [90]. Together, these data support the potential of ghrelin to promote food intake and body weight gain in patients with pulmonary cachexia.

5 Chronic heart failure

Chronic heart failure is a major public health problem affecting approximately 5 million Americans with nearly 500,000 new cases every year [91]. Cardiac cachexia is observed in 10–15% of patients with CHF [85] and cachexia in these patients is associated with a poor prognosis and an increased mortality rate compared to non-cachexia patients [92]. Accordingly, mortality rates in patients with CHF are as high as 50% in patients with cachexia compared to 17% in patients without cachexia [1, 92].

Left ventricular dysfunction and left ventricular remodeling (dilatation and wall thinning) are frequently observed in patients with advanced stages of CHF [86, 93]. Growth hormone and IGF-1 are important physiological regulators of myocardial growth and performance [94, 95] and patients with CHF show typically elevated serum levels of GH and normal to decreased levels of IGF-1 [96, 97], thus indicating that alterations of the GH/IGF-1 axis might be implicated in the myocardial dysfunction and cachexia in these patients. Several studies have assessed the therapeutic potential of GH supplementation in the treatment of CHF, revealing that GH treatment improves left ventricular dysfunction and cardiac performance in both CHF rats [98–100] and patients with CHF [101]. Due to ghrelins beneficial effects on energy metabolism and GH/IGF-1 secretion it is suggested that ghrelin might improve cardiac performance and cachexia in CHF patients through GH-dependent and -independent mechanisms [91, 102]. Accordingly, 3-week treatment of CHF rats with ghrelin (100 μg/kg/day) increased serum GH and IGF-1 levels and promoted body weight gain and improved cardiac performance by increasing the diastolic thickness of the non-infarcted posterior wall and by inhibition of left ventricular enlargement [102]. In line with these observations, twice-daily treatment of CHF patients with ghrelin at doses of 2 μg/kg for 3 weeks improved cardiac performance and attenuated cachexia by increasing muscle strength and lean body mass [10]. Ghrelin further inhibits apoptosis of cardiomyocytes and endothelial cells in vitro [103] and decreases arterial pressure while increasing cardiac output in CHF rats [102] and healthy humans [104]. Together, these data indicate that ghrelin has beneficial effects on cardiovascular performance and cachexia through GH-dependent and independent mechanisms and that modulation of the ghrelin system is an interesting target for the treatment of myocardial dysfunction and cachexia in patients with CHF.

6 Renal failure

Anorexia and cachexia are frequently observed in patients with chronically decreased renal function, such as in patients with ESRD or chronic kidney disease [105, 106]. Renal insufficiency in these patients is often accompanied by increased serum levels of pro-inflammatory cytokines, such as TNFα and IL-6 [105, 106], which promote tissue wasting and cachexia by, e.g., inhibition of myogenesis and stimulation of skeletal muscle protein breakdown [5, 7].

Plasma levels of desacyl- and total ghrelin are elevated in patients with renal failure [107–110] and decline upon dialysis treatment [109, 110]. As the kidney is the primary site of ghrelin clearance [111] it is likely that ghrelin accumulates in these patients as a result of renal insufficiency [13, 112]. Several studies have assessed the therapeutic potential of ghrelin in the treatment of anorexia and cachexia in patients with renal failure [112–114]. Continuous infusion of nephrectomized rats for 14 days with either ghrelin or ghrelin analogues (BIM-28125 and BIM-28131, 150 nmol/kg/day) significantly increased food

intake and lean body mass and tended to decrease overall pro-inflammatory cytokines compared to saline treated controls [112]. Accordingly, in a randomized, double blind, placebo-controlled crossover design, in which patients with peritoneal dialysis where treated with a single subcutaneous injection of ghrelin (3.6 nmol/kg), ghrelin increased immediate food intake by 57% compared to saline treated controls [113]. A similar effect on food intake was found in a double-blinded randomized crossover study where malnourished dialysis patients were treated for 1 week with 12 μg/kg/day of ghrelin [114].

7 Conclusion

Total ghrelin-like immunoreactivity in plasma is typically elevated in patients with anorexia nervosa as well as in cachexia associated with chronic heart failure [115, 116], renal failure [107, 117], chronic obstructive pulmonary disease [85, 89], and various forms of cancer [71, 118, 119]. Hyperghrelinemia in these patients may reflect a compensatory response to counteract the weight loss associated with skeletal muscle and fat mass wasting.

Several animal studies support the potential of ghrelin and ghrelin analogues to promote food intake and body weight gain in cachexia associated with heart failure [91, 102, 120, 121], chronic kidney disease [112] and cancer [67, 68, 70]. Accordingly, several human trials report improvements of appetite and body mass upon ghrelin treatment in patients with anorexia nervosa [64] and cachexia associated with renal failure [113, 114], chronic heart failure [10], chronic obstructive pulmonary disease [11], and cancer [73]. Notably, as yet all studies support the safety and tolerability of ghrelin treatment and no serious adverse side effects have so far been reported [73, 74]. Together, these data indicate that the endogenous ghrelin system represents an attractive target for the treatment of pathologically reduced body weight and tissue wasting, the key clinical feature of cachexia. However, further studies in larger populations are necessary to clarify the long-term effects of ghrelin treatment and to assess the possible impact of ghrelin and ghrelin induced growth factor release on tumor growth and carcinogenesis.

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