GHRELIN is a peptide hormone that was discovered in 1999 as an endogenous ligand for the growth hormone (GH)-secretagogue receptor (GHS-R) [1, 2]. Ghrelin, a 28-amino-acid peptide, possesses a unique fatty acid modification, an n-octanoylation, at Ser 3. Of the two circulating forms of ghrelin, acylated and unacylated (desacyl), the acylated form is thought to be essential for ghrelin’s biological activity through GHS-R. Recently, however, desacyl ghrelin was reported to influence both cell proliferation and adipogenesis through an unknown receptor different from GHS-R [2–5]. Ghrelin is mainly produced in the stomach and circulates in the blood at a considerable plasma concentration. Expression of ghrelin is also detectable in the hypothalamus, intestine, pituitary, placenta and other tissues [1, 3–5]. Ghrelin is now known to play a role in a number of different physiological processes. For example, ghrelin increases GH secretion, feeding, and body weight when administered centrally or peripherally (Fig. 1) [1, 6–15].

These unique effects of ghrelin and GHS should be invaluable for the development of novel treatments and disease diagnostic techniques [16–18]. Clinical trials have already been performed to assess the utility of GHS for the treatment of short stature [19], GH deficiency [19, 20], obesity [21] and catabolic conditions [22]. Several preliminary studies have also been performed to assess the possible benefits of ghrelin administration to humans [9–15, 23–26]. Because many excellent reviews concerning basic and clinical researches on ghrelin have already been published, we will summarize and discuss recent clinical trials of ghrelin in this work.

**Phase I studies**

In 2001, Nagaya et al. gave six healthy men either an intravenous bolus of human ghrelin (acylated form) (10 µg/kg) or placebo and then the opposite injection 1–2 wks later in a randomized fashion [12]. They found that the plasma total (acylated and desacyl) ghrelin level dropped with a half life of 10 min and that all study subjects tolerated this study protocol well, although ghrelin caused a slight warm feeling and drowsiness in four subjects. In 2003, we conducted a larger double-blinded, randomized, placebo-controlled trial in which the pharmacokinetics of both total and acylated ghrelin were analyzed simultaneously [27]. Eighteen male volunteers were randomly assigned into three groups of six subjects: members of the low- and high-dose ghrelin groups received intravenous injections of 1 and 5 µg/kg ghrelin (acylated form), respectively, and those in the placebo group were injected with mannitol instead of ghrelin. Acylated ghrelin disappeared more rapidly from the plasma than did total ghrelin, with elimination half-lives of 9–13 and 27–31 min, respectively. The number of subjects that experienced adverse effects did not significantly differ among the three groups, and all adverse effects were transient and well tolerated.
Among all studies analyzed, more than one hundred subjects have received ghrelin injections, and only mild adverse effects have been reported, including sensations of bowel movement, feelings of warmth, huger, somnolence, and hyperhidrosis [9–15, 23–26].

**Phase II studies**

1. **Appetite-related disorders**

Ghrelin is the first circulating hormone demonstrated to stimulate appetite in humans. Wren et al. showed that a 17 ng/kg/min intravenous infusion of ghrelin for 270 min enhanced appetite and food intake in humans [15]. Similarly, we found that ghrelin administration tended to increase the sensation of hunger in a dose-dependent manner, particularly in the early phase after injection, although the difference between groups was not statistically significant. In addition, whereas two of the six subjects in the placebo group did not show any change in the hunger score, all of the subjects in both the low- and high-dose groups reported increases. To confirm the orexigenic effect of ghrelin, either a crossover study or one analyzing larger groups will be necessary. In addition, because tests for appetite are subjective and variable among subjects, only double-blinded studies such as that described here will yield reliable findings.

1) **Cachexia**

Cachexia manifests with excessive weight loss in the setting of ongoing disease including congestive heart failure (CHF), cancer, chronic obstructive pulmonary disease (COPD) and severe inflammation [28]. Anorexia is among the major causes of weight loss in cachexia. Loss of appetite and loss of weight are major causes of morbidity and mortality affecting many patients with anorexia-cachexia syndrome. There is a strong and immediate need for more effective and better-tolerated appetite stimulatory treatments. Several trials have already been performed to explore the utility of ghrelin in the treatment of cachexia. Circulating ghrelin levels are elevated in patients with cachexia, compared with normal-weight control subjects, reflecting the state of negative energy balance [29–32].

Nagaya et al. investigated the effects of ghrelin on cardiac cachexia in patients with CHF [33]. A three-week administration of ghrelin (2 µg/kg twice a day) significantly increased food intake and tended to increase body weight. Moreover, they demonstrated improvement in exercise capacity, muscle wasting and
left ventricular function. Ghrelin treatment resulted in a significant decrease in plasma norepinephrine. Although this study was neither randomized nor placebo-controlled, eight patients with CHF who did not receive ghrelin (control group) were studied to exclude time-course effects during hospitalization. All of the aforementioned parameters remained unchanged in the patients with CHF who did not receive ghrelin therapy.

Anorexia is frequently encountered in cancer patients, and is one of the major causes of malnutrition and eventually cachexia. Neary et al. performed an acute, randomized, placebo-controlled, cross-over clinical trial to determine whether ghrelin stimulates appetite in seven cancer patients with anorexia [34]. A marked increase in energy intake (31 +/- 7%; P = 0.005) was observed with ghrelin infusion (17 ng/kg/min intravenous infusion of ghrelin for 270 min) compared with saline control, and every patient in the study increased food consumption. The meal appreciation score was higher by 28 +/- 8% (P = 0.02) in ghrelin-treated individuals.

The ability of ghrelin to improve cachexia and functional capacity in patients with COPD has been studied in an open-label pilot study in which ghrelin (2 µg/kg bid) was administered intravenously to seven cachectic patients with COPD for three weeks [35]. Repeated administration of ghrelin resulted in a significant increase in food intake, body weight, lean body mass and peripheral and respiratory muscle strength. Ghrelin attenuated the exaggerated sympathetic nerve activity, as indicated by a marked decrease in plasma norepinephrine level. Thus, treatment with ghrelin improved appetite, body composition, muscle wasting, functional capacity, and sympathetic augmentation in cachectic patients with COPD.

Finally, ghrelin may have a beneficial effect on anorexia in sepsis. In an animal model of excessive inflammation, septic shock, and wasting syndrome, repeated ghrelin treatment (twice daily for five days) increased food intake and body weight [36]. Although no clinical trial has been attempted in patients with sepsis, these findings suggest the therapeutic potential of the anti-wasting effects of ghrelin.

2) Anorexia nervosa (AN) and its related disorders

Anorexia nervosa (AN) is an eating disorder characterized by chronically decreased caloric intake, resulting in self-induced starvation. Plasma ghrelin levels are elevated in lean patients with anorexia nervosa, consistent with a state of negative energy balance [37–39]. Only a few preliminary studies have been performed to examine the effects of ghrelin in individuals with AN. Miljic et al. infused ghrelin (300-min intravenous infusion of 5 pmol/kg/min ghrelin) into nine AN patients with very low body weights six AN patients who had partially recovered their body weight but were still amenorrheic, and ten constitutionally thin female subjects [40]. The fifteen AN patients felt significantly less hungry compared with the constitutionally thin subjects, suggesting that AN patients are less sensitive to the orexigenic effects of ghrelin compared with healthy controls. In another paper, however, six of nine patients with restrictive AN were reported to be hungry after ghrelin administration (1.0 µg/kg as an intravenous bolus) which was a similar ratio to that seen in normal subjects (five of seven) [41]. Clearly, further studies, including randomized controlled trials, are needed to determine whether ghrelin is useful for the treatment of AN.

Functional dyspepsia (FD) is a disorder characterized by the presence of chronic or recurrent symptoms of upper abdominal pain or discomfort [42]. Although no known specific organic abnormalities are present in FD, abnormalities in gastrointestinal motility and sensitivity are thought to play a role in a substantial subgroup of patients. In addition, some patients also suffer from anorexia and body-weight loss. Therefore, we are currently examining whether repeated ghrelin administration increases food intake in FD patients. We found that plasma acylated, but not desacyl ghrelin, levels were correlated with a subjective symptom score in FD patients, suggesting that acylated ghrelin may play a role in the pathophysiology of FD [43].

2. GH deficiency-related disorders

Strong stimulation of GH secretion by ghrelin has been well demonstrated in humans [9–13, 17, 27]. As with GHS, ghrelin may be useful for the diagnosis and treatment of short stature and GH deficiency. Elderly individuals would be particularly suitable candidates for ghrelin treatment. Aging is associated with progressive decreases in GH secretion, appetite and energy intake [44–47]. This reduced GH secretion is called “somatopause” and may be a cause of age-related metabolic and physiologic changes including reduced lean body mass and expansion of adipose
mass. Sarcopenia is associated with functional decline and death. Altered blood lipid profiles also favor the development of vascular diseases that may increase overall mortality. The age-related reduction in energy intake has been termed “the anorexia of aging” and predisposes to the development of under-nutrition, which has been implicated in the development and progression of chronic diseases commonly affecting the elderly, as well as in increasing mortality. Growth hormone therapy increases IGF-I levels, promotes anabolism and increases muscle strength in healthy elderly individuals, as well as in selected patient groups [48–50]. Therefore, ghrelin and GHS may also have therapeutic potential to assist in the recovery of frail patients who require nutritional support and conventional rehabilitation [51]. Indeed, we are currently evaluating whether repeated ghrelin administration during the perioperative period would promote functional recovery in elderly patients undergoing elective total hip replacement.

We found that plasma levels of acylated ghrelin in healthy elderly female subjects tended to be low and were correlated positively with IGF-1 levels, suggesting that the negative feedback mechanism does not function properly in elderly subjects [52]. Further, acylated ghrelin concentrations in elderly females correlated with both systolic blood pressure and the frequency of bowel movements. These findings suggest that, in elderly females, acylated ghrelin may play a role in the regulation of the GH/IGF-1 axis, blood pressure and bowel movements.

3. Other disorders

Reflecting the wide expression patterns of both ghrelin and its receptor, this peptide is now known to play a role in a number of different physiological processes including cardiovascular function, cellular proliferation and differentiation, gastric motility and acid secretion, pancreatic exocrine and endocrine function as well as on glucose metabolism, sleep and behavior, and immune regulation. For example, as we mentioned above, repeated administration of ghrelin in patients with CHF significantly improved left ventricular function as well as food intake. A large number of studies have been vigorously performed to elucidate the various activities of ghrelin by many investigators all over the world. We believe that some of these may lend support to the development of novel clinical applications of ghrelin in the future.

Epilogue

Since the discovery of ghrelin, more than six years have passed and abundant evidence supporting its variety of functions has accumulated. In parallel, clinical trials have begun and proceeded to exploit these activities in the treatment and diagnosis of human disease. There are several characteristic features of the clinical applications of ghrelin; 1) the multiplicity and uniqueness of its function, 2) the unique structure with fatty acid modification, and 3) the paucity of severe adverse effects. These characteristics should allow us to develop novel and unique therapies for a variety of disorders, including many currently intractable and serious diseases. Indeed, translational research into the clinical applications of ghrelin is a challenging and potentially rewarding avenue for the future.

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