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Actions and therapeutic pathways of ghrelin for gastrointestinal disorders

Michael Camilleri, Athanasios Papathanasopoulos, and Suwebatu T. Odunsi

Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.), College of Medicine, Mayo Clinic, Rochester, MN, USA (M. Camilleri, A. Papathanasopoulos, S. T. Odunsi)

Abstract

Ghrelin is a peptide hormone that possesses unique orexigenic properties. By acting on the growth-hormone secretagogue receptor 1a, ghrelin induces a short-term increase in food consumption, which ultimately induces a positive energy balance and increases fat deposition. Reduced ghrelin levels have been observed in obese patients and after bariatric surgery. In particular, bariatric procedures that involve gastric resection or bypass lead to reduced ghrelin levels. Administration of physiological doses of exogenous ghrelin to humans does not significantly alter gastric motility; however, administration of high doses stimulates gastric motility, with increased gastric tone and emptying, and increased activity of migrating motor complexes in the small bowel. The potential of ghrelin agonists to be used as prokinetics is being tested in patients with gastroparesis and postoperative ileus. Ghrelin acts directly on pancreatic islet cells to reduce insulin production. Findings from studies in animals have revealed that small-molecule ghrelin antagonists favorably influence glucose tolerance, appetite suppression and weight loss. Other studies have demonstrated that ghrelin antagonists retard gastric emptying only at very high doses, which suggests that these agents will probably not induce upper gastrointestinal symptoms. The potential of this new class of therapeutic agents to influence appetite and glycemic control strongly indicates that they should be tested in clinical trials.

Introduction

Ghrelin is a hormone found mainly in the stomach. The actions of ghrelin are primarily orexigenic—to stimulate appetite, increase energy stores and promote the deposition of adipose tissue. The ability of ghrelin to modulate energy balance and alter intestinal motility suggests that modification of ghrelin signaling pathways might be beneficial for patients with gastrointestinal disorders or obesity. This hypothesis has led to the development of agents that pharmacologically modulate ghrelin receptors. This Review discusses key issues in relation to the role of ghrelin in gastrointestinal motor function, obesity and the metabolic syndrome. Alterations in levels of ghrelin that are observed following bariatric surgery and drug manipulations are also discussed, and the effects of ghrelin agonists and a new class of therapeutic agents, the small-molecule ghrelin-receptor antagonists, are described.

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Correspondence: M. Camilleri, Mayo Clinic, Charlton 8–110, First Street S.W., Rochester, MN 55905, USA, camilleri.michael@mayo.edu.

Competing interests

The authors declare no competing interests.

Function and metabolism of ghrelin

Function

Ghrelin is a 28-amino acid peptide that is acylated at its third serine residue with an octanoyl group. The amino acid sequence of ghrelin is 36% homologous with that of motilin, a hormone with a known ability to modulate gastric motor activity.¹ Ghrelin was originally identified in 1999 as the endogenous ligand of the growth-hormone secretagogue receptor 1a (GHS-R1a),² a G-protein-coupled receptor that was first cloned from hypothalamic tissue.³ GHS-R1a was the prototype of a class of receptors that were of particular interest because of their ability to induce the release of pituitary growth hormone following their activation by synthetic peptides. The ligands for these receptors were collectively termed the growth-hormone secretagogues.⁴ By acting on their corresponding receptor, these ligands directly stimulate growth-hormone release from the pituitary gland, rather than via the conventional pathway mediated by growth-hormone-releasing hormone. For the purpose of clarity, this Review uses the terms 'ghrelin receptor' to refer to the GHS-R1a, 'ghrelin agonist' to refer to exogenous GHS-R1a receptor ligands, and 'ghrelin antagonists' for antagonists of the GHS-R1a receptor.

In addition to stimulating growth-hormone release, the administration of exogenous ghrelin induces a robust feeding response⁵ and influences energy homeostasis. Ghrelin also exerts effects on the adrenal gland and the pituitary–gonadal axis and is involved in regulation of the immune system, osteoblast function, the cardiovascular system and neoplastic cell proliferation in several types of cancers (for example, lung, breast, pituitary and thyroid [Figure 1]).^{6–8} Ghrelin also significantly increases expression levels of insulin-like growth factor I (IGF-I) and fat-free mass in elderly individuals, which suggests that this hormone might have a role in the reversal of sarcopenia.⁹ The focus of this Review, however, is the effects of ghrelin on gastrointestinal function, glycemic control and the metabolic syndrome, and properties relating to other actions of ghrelin will not be discussed further.

Location of ghrelin and its receptor

Ghrelin has been identified in all human tissues studied, but 80–90% of ghrelin is located in the stomach, where it is produced by ghrelin-producing endocrine cells. Endocrine cells located in the human oxyntic mucosa include enterochromaffin cells, which produce 5-hydroxytryptamine or histamine, somatostatin-producing cells (D cells), and X/A cells, which secrete unknown products. The ghrelin-producing cells in the stomach resemble X/A cells, and in fact, some X/A cells may produce ghrelin.¹⁰

A small ghrelin 'reservoir' is located in the central nervous system, namely in the arcuate nucleus and in a group of neurons that are located adjacent to the third ventricle in the hypothalamus. Both of these central sites are involved in the regulation of appetite.^{11,12}

The ghrelin receptor is also widely expressed. In the brain, it is predominantly expressed in the arcuate nucleus, and peripherally, it has been identified in the stomach, intestine and pancreas.^{3,13} Circulating ghrelin probably crosses the blood–brain barrier to reach its central targets.¹⁴ Alternatively, ghrelin might indirectly activate neurons in the arcuate nucleus, possibly via vagal signaling.¹⁵ However, findings from studies in patients who have undergone vagotomy indicate that induction of growth-hormone secretion by ghrelin might not involve afferent vagal stimulation, and thus the mechanisms by which ghrelin exerts its actions are not completely understood.¹⁶

Other products of the ghrelin gene

The human ghrelin gene is located on chromosome 3p and comprises five exons and three introns; the first exon is noncoding. Ghrelin is derived from the ghrelin gene by alternative splicing and extensive post-translational enzymatic modification from the sequential precursor peptides, preproghrelin and proghrelin.¹⁷ In addition to ghrelin, other peptides are also produced by alternative splicing and post-translational modification of the ghrelin gene product. Desacyl ghrelin is produced from the cleavage of proghrelin, and is the major circulating form of ghrelin. This peptide lacks the octanoyl group, which is essential for binding to the ghrelin receptor.¹⁸ Cleavage of proghrelin also produces a 66-amino acid tail, which may either circulate as a full-length peptide (c-ghrelin),¹⁹ or be processed to produce small peptides, including a 23-amino acid peptide called obestatin.

Obestatin was first identified in mice by Zhang *et al.*,²⁰ who described the inhibitory effects of this peptide on food intake, gastric emptying *in vivo* and jejunal muscle contractions *in vitro*. Another study, however, was unable to replicate these findings.²¹ Furthermore, no evidence of circulating obestatin peptides in humans and rats, or in rat tissue, has been found.^{21,22}

Ghrelin metabolism

As mentioned earlier, almost 90% of ghrelin circulates in the blood as desacyl ghrelin. This peptide is not octanoylated and, therefore, does not bind to the ghrelin receptor. Instead, it binds to an as-yet-uncharacterized receptor.²³ Studies have demonstrated subtle and sometimes contradictory biological actions of desacyl ghrelin in the control of food intake,²⁴ glucose²⁵ and lipid²⁶ metabolism, gastrointestinal motor function²⁷ and cellular proliferation.²⁸ These effects usually oppose or modify the actions of ghrelin.

The enzyme that catalyzes the octanoylation of desacyl ghrelin at Ser3 to produce active ghrelin was identified in 2008 as ghrelin O-acyltransferase (GOAT),²⁹ a member of the superfamily of membrane-bound O-acyltransferases. The discovery of GOAT provides a putative, selective target through which to inhibit the biological actions of ghrelin by prevention of its activation by octanoylation. GOAT inhibitors might, therefore, prevent the development of diet-induced obesity or be used to treat patients with type 2 diabetes by preventing the inhibition of insulin secretion and sensitivity by ghrelin.³⁰

Fluctuations in circulating levels

Plasma levels of ghrelin increase with prolonged fasting—an effect that is reversed by an intragastric infusion of glucose.³¹ Circulating levels of ghrelin surge shortly before scheduled meals and are suppressed by ingested nutrients. Carbohydrates have the greatest suppressive effect, followed by proteins, with fats having the least effect on ghrelin levels.³² The control of preprandial ghrelin secretion remains incompletely understood; however, the actions of sympathetic nerves, endothelin and secretin might be involved.³³

Postprandial ghrelin suppression has been documented in many animal species and in human adults, but not in children.³⁴ The mechanism by which ghrelin is suppressed postprandially is also unclear. Postprandial ghrelin suppression seems to result, at least in part, from neurally transmitted intestinal signals that are not mediated through vagal pathways and are augmented by the presence of insulin. Suppression of plasma ghrelin levels is observed after administration of oral or intravenous glucose loads in healthy individuals and in patients with type 2 diabetes mellitus after intake of a meal, but not after gastric distention.^{35,36} However, postprandial ghrelin suppression was not observed in patients who had undergone subdiaphragmatic vagotomy or total gastrectomy.³⁶ These data suggest that in healthy individuals, postprandial ghrelin suppression may be partially

mediated by vagal mechanisms, since suppression was absent with vagotomy. However, a nongastrointestinal mechanism probably explains the suppression of ghrelin observed after intravenous administration of glucose. The expression of ghrelin receptors in the stomach, hypothalamus and pituitary gland is also dependent on the satiety and energy status of an individual.³⁷

Regulation of energy homeostasis

Ghrelin acts as an orexigenic factor, independent of the degree of satiety³⁸ and growth-hormone secretion³⁹ in many species, including humans.⁴⁰ The orexigenic actions of ghrelin are believed to be mediated at least in part via central activation of neuropeptide Y pathways,⁴¹ which causes a short-term increase in food intake.

In addition, ghrelin can act as a medium-term and long-term regulator of energy homeostasis by increasing fat deposition and inducing a positive energy balance. Ghrelin levels increase during diet or disease-induced weight loss.⁴² Obese children and adults have lower fasting ghrelin levels and exhibit smaller postprandial changes in ghrelin levels than do age-matched controls of a normal weight.⁴³ Ghrelin serum levels are also inversely correlated with age and concentrations of serum insulin.⁴⁴ In contrast with studies in obese people, a study in mice by Asakawa *et al.* demonstrated that fasting expression levels of ghrelin messenger RNA (mRNA) in the mouse stomach were increased by a high-fat diet.⁴⁵ In this study, ghrelin reportedly induced adiposity in a dose-dependent manner, elevated blood glucose and decreased insulin production.⁴⁵ Ghrelin also elevated leptin mRNA levels and reduced expression levels of resistin mRNA.⁴⁵ Thus, modulation of serum ghrelin by fat intake is species-dependent, but the orexigenic effects of ghrelin are consistent in mice and humans.

In a randomized, placebo-controlled trial, Strassburg *et al.* administered either human ghrelin or one of two ghrelin agonists (BIM-28125 and BIM-28131) to rats by continuous subcutaneous infusion for 2 weeks in doses either intended to mimic physiological doses, or at high, 'pharmacological' doses.⁴⁶ Physiological doses had no effect on body weight or body composition. The high doses of ghrelin and ghrelin agonists induced weight gain in rats by promotion of fat deposition and, to a lesser extent, lean-mass gain. All the above-described medium-term and long-term effects of ghrelin are thought to be mediated via AgRP-mediated pathways in the hypothalamus. Of note, neuropeptide Y and AgRP pathways interact in the hypothalamus to control energy homeostasis.⁴⁷ The ghrelin system also interacts with other complex brain-peptide pathways to control food consumption and energy homeostasis; these relationships are reviewed in detail elsewhere.⁴⁸

Regulation of gastric motility

The potential therapeutic effects of ghrelin and its agonists have been investigated in three clinical scenarios. First, for the treatment of gastrointestinal diseases, such as postoperative ileus and gastroparesis;⁴⁹ second, as an alternative to exogenous growth-hormone administration in children or to enhance growth-hormone secretion with an aim to increase lean mass in otherwise healthy adults;^{9,50} third, to control appetite and eating disorders and in patients with cardiac cachexia.⁵⁰

The rationale for using ghrelin to treat gastrointestinal diseases is based mainly on its effects on gastric motility. The effects of an intravenously administered ghrelin agonist, TZP-101, were evaluated in a phase I trial in humans, which showed promising results in terms of its safety and its pharmacokinetic and pharmacodynamic profiles.⁵¹ In animal studies, TZP-101 accelerated the gastric emptying of liquids in rats.⁵² Phase II trials are in progress to investigate the effects of TZP-101 in patients with postoperative ileus or severe

gastroparesis. Another ghrelin agonist that is administered orally, TZP-102, is also under evaluation for the treatment of chronic gastroparesis.⁵³

Administration of a growth-hormone secretagogue and a ghrelin mimetic (MK-677) to healthy elderly individuals increased levels of growth hormone and IGF-I to those observed in healthy young adults. The treatment was well tolerated and increased fat-free mass;⁹ however, no benefit to quality of life was noted. In addition, MK-677 increased insulin resistance and blood glucose levels. The results from this study should, however, be interpreted with caution, because of the small sample size and relatively short duration of treatment.

The potentially increased risk of cancer associated with chronic growth-hormone secretagogue therapy is cause for concern. Ghrelin and its receptors are expressed in several tumor and neoplastic cell lines, which suggests a possible autocrine or paracrine role for ghrelin in neoplasm development.⁵⁴ Moreover, activation of the growth hormone–IGF-I axis may predispose an individual to cancer, because the IGF receptor has a role in cancer development, growth and metastasis.⁵⁵ On the other hand, a reassuring finding is that in elderly individuals, MK-677 not only increased the production of IGF-I, but also modestly increased production of the IGF-I-binding proteins, which act to inhibit the proliferative effects of IGF-I. In elderly mice, administration of a growth-hormone secretagogue actually inhibited metastatic tumor growth.⁵⁶ Ghrelin also exerts antiproliferative effects in various human tumor cell lines, derived from thyroid cancer, small-cell lung cancer, and breast carcinoma; however, ghrelin exerts proliferative actions in prostate, hepatoma and pancreatic carcinoma cell lines.⁵⁷ Long-term studies are, therefore, required for all ghrelin agonists, with careful selection of patients before initiation of therapy to enable a full examination of the safety profile of this class of therapeutic agents.

Effects of ghrelin agonists on gastric motility

Findings from studies in animals have revealed that ghrelin stimulates gastric motor function by acting at several levels: by vagal signaling, directly within the enteric nervous system, or by effects on vagal function within the central nervous system after crossing the blood–brain barrier (Figure 2). Intravenous administration of a 0.2 µg/kg dose of exogenous ghrelin to healthy individuals does not increase levels of circulating growth hormone above those observed physiologically.⁵⁸ This dose of ghrelin is, therefore, considered to be a physiological dose; however, most reported studies have used pharmacological doses that are 100–1,000 times higher than physiological doses.^{58,59}

Studies in healthy volunteers—A study by Tack *et al.* used an antroduodenal manometry catheter together with a barostatically controlled balloon that was placed in the gastric fundus to investigate the effect of ghrelin administration on upper gastrointestinal motility in nine healthy individuals.⁶⁰ The administration of 40 µg ghrelin as an intravenous infusion over a 30 min interval induced premature onset of phase III of the migrating motor complex, and increased proximal gastric tone. These effects are similar to those induced by intravenously administered motilin. However, given the lack of crossreactivity in cell lines that express the receptors for both peptides,⁶¹ the actions of ghrelin seem to be independent of the actions of motilin or its receptors.

Our group has measured gastric volume following the administration of ghrelin to healthy volunteers by using single photon emission CT (SPECT).⁵⁸ Intravenous bolus administration of 0.33 µg/kg ghrelin produced physiological levels of circulating growth hormone, but resulted in only a slight, albeit significant, reduction in fasting gastric volumes compared with those measured in patients given a placebo. Ghrelin administration had no significant effect on the gastric emptying of solids or gastric accommodation volumes. The

fixed dose administered to patients in the study by Tack *et al.*⁶⁰ was approximately twice the physiological dose administered in the SPECT study.⁵⁸ Thus, the contrasting results obtained by these two studies could arise from the different ghrelin doses that were administered. Of note, an *in vitro* study that investigated the effects of ghrelin on isolated gastric smooth-muscle strips obtained from diabetic mice with gastroparesis also failed to demonstrate a role of ghrelin in the induction of muscle contractions.⁶²

Studies in patients with gastroparesis—The potential of ghrelin to act as a prokinetic drug for the treatment of gastroparesis has been tested in several clinical studies (Table 1). In one double-blind, placebo-controlled, crossover study, 10 patients with diabetes and symptoms of gastroparesis received an intravenous infusion of saline or ghrelin (5 pmol · kg⁻¹/min) for a period of 2 h on two separate occasions.⁶³ The rate of gastric emptying after a rice-pudding meal was recorded using serial abdominal ultrasound scans. Ghrelin increased gastric emptying in seven of the 10 patients from 30 ± 6% emptied 2 h after administration of saline to 43 ± 5% after treatment with ghrelin.⁶³

Other studies have investigated the effects of ghrelin administration in patients with idiopathic and diabetic gastroparesis and in patients with gastroparesis that arose secondary to vagotomy. These studies demonstrated a similar acceleration of gastric emptying to that described above.^{64–66} However, some studies have reported mixed results or that administration of ghrelin to patients with gastroparesis had no effect on gastric emptying.^{63,65}

All the above-described studies have used small sample sizes and employed different methods to measure gastric emptying. The conflicting results obtained in these clinical studies^{63–66} might, therefore, be explained by variations in the doses of ghrelin administered or by other methodological differences, such as the method used to measure gastric emptying (Table 1). In general, data suggest that stimulation of ghrelin receptors by use of high pharmacological doses of ghrelin might accelerate gastric emptying, induce contraction of the human gastric fundus and/or reduce fasting gastric volume.

The effect of ghrelin agonists on symptoms in patients with gastroparesis, however, requires further study. Murray *et al.* did not observe any increase in bloating, hunger or nausea following the administration of ghrelin,⁶³ while Tack *et al.* demonstrated that the administration of ghrelin decreased the cumulative meal-related symptom score and individual scores for fullness and pain.⁶⁴

Future studies will need to compare the benefits and potential risks of using ghrelin agonists with other pharmacological agents for the treatment of gastric motility disorders. For example, the new class of 5-hydroxytryptamine receptor 4 (5-HT₄) agonists (for example, prucalopride and TD-5108), have greater selectivity for 5-HT₄ receptors relative to *KCNH2* channels (also known as H-ERG channels), and seem to stimulate gastric emptying. The selectivity of these agonists indicates they should have improved safety from a cardiac perspective compared with previous 5-HT₄ agents, such as cisapride. The relative effectiveness of ghrelin agonists and this new class of compounds remains to be elucidated.

Ghrelin antagonists and gastric motility

Findings from a study in which ghrelin administration stimulated the production of growth hormone to levels within the normal range suggest that, at these physiological levels, ghrelin does not significantly alter gastric accommodation or emptying, but does have a moderate effect on fasting gastric volumes.⁵⁸ These data suggest that the ghrelin receptor does not have a pivotal role in the control of baseline gastric function and, therefore, that inhibition of ghrelin receptors by use of ghrelin antagonists would not be predicted to considerably impair

gastric motor function. Studies that have investigated the effects of administration of a new class of agent—the small-molecule ghrelin-receptor antagonists—to animals support this interpretation; only very high doses of these agents delayed gastric emptying. By contrast, low doses of ghrelin antagonists had effects on body weight, but did not impair gastric emptying.^{45,67}

Regulation of glucose homeostasis

Insights from studies with ghrelin agonists

Experimental studies in humans and animals support a direct role for ghrelin in the regulation of glucose homeostasis by activation of ghrelin receptors located in the pancreas (Figure 2). Ghrelin and its receptor are both expressed in pancreatic islet cells.^{68,69} Ghrelin has been demonstrated to suppress insulin secretion *in vitro* and *in vivo* and cause an increase in plasma levels of glucose in rodents⁷⁰ and in humans.⁷¹ One study investigated the effects of intravenous ghrelin administration to patients who had previously undergone gastrectomy or vagotomy. Compared with patients who received an intravenous infusion of saline, the administration of ghrelin during a hyperinsulinemic euglycemic clamp procedure reduced endogenous insulin secretion (demonstrated by reduced C-peptide levels) and reduced the rate of glucose disposal.⁷² Chronic administration of small-molecule ghrelin agonists to healthy, elderly individuals induces hyperglycemia and insulin resistance.⁷³ Conversely, ablation of ghrelin signaling improves glucose tolerance and enhances insulin secretion in leptin-deficient ob/ob mice.⁷⁴

Despite findings from several studies that support a role for ghrelin in the control of glucose homeostasis, conflicting reports also exist with regard to differences between species and in feeding status. For example, a study performed in sheep aimed to define the role of ghrelin further in the control of glucose-mediated insulin secretion in relation to feeding status and energy balance.⁷⁵ A hyperglycemic clamp was established with a continuous titration of glucose to examine the effect of ghrelin on the glucose-induced insulin response during fasting and after feeding. In the fasting state, administration of a synthetic ghrelin antagonist significantly enhanced glucose-induced insulin secretion; this finding is consistent with observations in small animals, such as rodents, in which ghrelin reduces insulin secretion.⁷⁰ However, in the fed state, intravenous administration of synthetic, ovine ghrelin during a hyperglycemic clamp also significantly enhanced glucose-induced insulin secretion—an effect that was suppressed by subsequent treatment with a ghrelin antagonist. These data suggest that ghrelin acts to inhibit or stimulate glucose-induced insulin secretion in the fasting and fed states, respectively. These actions of ghrelin are probably directly mediated by ghrelin receptors located in the pancreas. This hypothesis of the mechanism of ghrelin action is supported by a series of experiments performed in normal, gastrectomized and ghrelin-knockout mice, which demonstrated that ghrelin derived from the pancreatic islet cells is a physiological regulator of glucose-induced insulin release (Figure 3).⁷⁶

The majority of studies that have explored the role of desacyl ghrelin in glucose metabolism have found that this alternative product of the ghrelin gene counteracts or modifies the actions of ghrelin. As mentioned earlier, the receptor to which desacyl ghrelin binds has not yet been identified; however, findings from studies that used isolated mouse and rat pancreatic islet cells suggest that desacyl ghrelin regulates glucose metabolism without affecting hormone secretion by the pancreas. Several lines of evidence indicate that desacyl ghrelin counteracts the effects of ghrelin on insulin secretion. Administration of desacyl ghrelin to isolated islet cells of rodents at a 10-fold greater concentration than that of ghrelin inhibits the ability of ghrelin to reduce insulin secretion.²⁵ Intravenous administration of desacyl ghrelin to normal, healthy individuals completely blocks the hyperglycemic effects of a bolus ghrelin injection.⁷⁷ Finally, desacyl ghrelin inhibits glucose output from isolated

pig hepatocytes and counteracts the stimulatory effect of ghrelin on hepatocyte glucose output.⁷⁸

Ghrelin also seems to promote the survival of pancreatic β -cells by mechanisms other than ghrelin-receptor activation; administration of ghrelin inhibited apoptosis in a pancreatic β -cell line via MAPK–PI3K pathways.⁷⁹ Ghrelin and desacyl ghrelin also promoted proliferation and inhibited β -cell apoptosis in a β -cell line and in human islets of Langerhans via cAMP–PKA, ERK1–ERK2, and PI3K–Akt signaling pathways.²⁸

Insights from animal models

The investigation of ghrelin and ghrelin-receptor knockout mice has not provided clear insight into the effect of ghrelin receptors on body weight. For example, the administration of exogenous ghrelin to ghrelin-receptor knockout (GHSR^{-/-}) mice did not stimulate appetite or growth-hormone release.⁸⁰ Normal ‘wild-type’, ghrelin knockout (ghrelin^{-/-}) and GHSR^{-/-} mice do not significantly differ in terms of body weight or growth rate.⁸⁰ Deletion of the ghrelin or ghrelin-receptor gene did not prevent diet-induced obesity or weight gain after weight loss.⁸¹ Weight loss with caloric restriction was identical between wild-type, ghrelin^{-/-} and GHSR^{-/-} knockout mice, despite the fact that blood glucose levels under caloric restriction were lower in knockout mice than they were in wild-type mice.⁸¹ However, ghrelin^{-/-} mice have increased glucose-induced insulin secretion and improved peripheral insulin sensitivity, which is consistent with the demonstrated ability of ghrelin to reduce insulin secretion.⁷⁴

Findings from knockout studies can be misleading, however, because compensatory mechanisms might be switched on to replace the function of the removed gene. Compensatory mechanisms for appetite and weight regulation probably account for some of the unexpected findings from the above-described knockout studies. To summarize the findings from this somewhat conflicting pool of data, ghrelin seems to be important for glucose homeostasis and insulin sensitivity, but might not be important for the regulation of growth and body weight. The presence of compensatory mechanisms that regulate appetite and weight cannot be excluded.

Insights from studies with ghrelin antagonists

Pharmacological antagonism of pancreatic ghrelin receptors in rats with diet-induced glucose intolerance enhanced insulin release and normalized glycemic control.⁷⁶ A growing body of evidence from studies in rodents indicates that small-molecule ghrelin-receptor antagonists enhance glucose homeostasis, insulin release and sensitivity, and induce weight loss in situations of energy excess. The authors of a comprehensive study in rats, which involved *in vivo* and *in vitro* investigations, reported that the ghrelin antagonist, YIL-870, completely blocked the dose-dependent, ghrelin-induced suppression of insulin secretion from dispersed rat islet cells.⁶⁷ A single, oral dose of YIL-870 improved glucose homeostasis during an intraperitoneal glucose tolerance test in rats.⁶⁷ The effects of YIL-870 were similar to those of a positive control—liraglutide, an antagonist of the human glucagon-like peptide 1 receptor, which also normalizes blood glucose. The improvement in glucose homeostasis observed after administration of YIL-870 was accompanied by increased insulin secretion. On the other hand, the effect of YIL-870 on fasting glucose was less than that induced by a rapid-onset sulfonylurea, nateglinide.⁶⁷ This finding suggests that the small-molecule ghrelin-receptor antagonists may be less effective inducers of islet-cell insulin secretion during fasting than they are postprandially. Ghrelin-receptor antagonists such as YIL-870 might, therefore, act specifically to reduce glucose in the fed state, but reduce the risk of hypoglycemia in the fasted state. The same study also reported that daily oral administration of YIL-870 led to reduced food intake and resulted in weight loss of up

to 15% of pretreatment weight, caused by the selective loss of fat mass in diet-induced obese mice.⁶⁷ Comparison with the cannabinoid 1 receptor antagonist, rimonabant, demonstrated that YIL-870 induced a longer-lasting weight reduction and a more sustained reduction of food intake. Findings from pair-feeding experiments indicated that the weight loss induced by YIL-870 was largely a consequence of reduced food intake.⁶⁷

At the highest tested dose (10 mg/kg), YIL-870 caused a modest delay in gastric emptying in obese mice. The magnitude of this effect was comparable to that induced by the positive control, the glucagon-like peptide 1 analog, exendin-4. At doses that improved glycemic control and weight loss, however, YIL-870 had no effect on gastric emptying. These findings indicate that delayed gastric emptying is not required for YIL-870 to induce weight loss.⁶⁷

The influence of ghrelin antagonists on energy balance has also been evaluated by Asakawa *et al.* in lean mice, diet-induced obese mice, and ob/ob mice.⁴⁵ Repeated administration of a small-molecule ghrelin-receptor antagonist decreased weight gain and improved glycemic control in the leptin-deficient and diet-induced obese mice—an effect that was not observed in the lean mice. The authors concluded that ghrelin activity is closely related to excess weight gain, adiposity and insulin resistance, particularly in situations of energy excess (for example, in animals fed a high-fat diet).⁴⁵ Together, the findings from these studies suggest that ghrelin antagonists might have potential therapeutic applications for the treatment of patients with type 2 diabetes or metabolic syndrome.

Effect of bariatric surgery on ghrelin

Surgical approaches to manage morbid obesity result in gastric restriction and/or intestinal malabsorption. Procedures that cause gastric restriction include laparoscopic vertical-banded gastroplasty, laparoscopic adjustable gastric banding and sleeve gastrectomy.⁸² Procedures that cause intestinal malabsorption include biliopancreatic diversion and biliopancreatic diversion with a duodenal switch. The Roux-en-Y gastric bypass procedure has features of both gastric restriction and intestinal malabsorption.⁸³

The long-term efficacy of laparoscopic adjustable gastric banding compared with conventional pharmacological and lifestyle interventions for reducing weight in patients with mild to moderate obesity was demonstrated in a randomized, controlled trial.⁸⁴ In this study, the weight loss achieved by the conventional and surgical interventions after 6 months was identical; patients in both groups lost 13.8% of their pretreatment weight. However, while the surgical-intervention group continued to lose weight—patients in this group achieved a mean loss of 21.6% of their pretreatment weight after 2 years—the nonsurgical intervention group progressively regained weight, which resulted in a mean weight loss of just 5.5% after 2 years.

The prospective, controlled Swedish Obese Subjects Study investigated the efficacy of bariatric surgery compared with that of pharmacological interventions for weight loss. This trial had a follow-up period of 12 years, and reported similar findings to those described above.^{85,86} This study found that body weight stabilized 8–9 years after all types of surgical interventions investigated. The greatest weight reductions were achieved by gastric bypass, while the least effective method was laparoscopic adjustable gastric banding.

The effects of diet and Roux-en-Y gastric bypass on the levels and diurnal profile of endogenous ghrelin was investigated by Cummings *et al.*⁸⁷ Diet induced an average loss of 17% of initial body weight after 6 months, and was associated with a significant increase in plasma levels of ghrelin over a 24 h period. By contrast, despite a loss of 36% of pretreatment body weight in patients after Roux-en-Y gastric bypass, levels of plasma

ghrelin were significantly lower in this group of patients than in normal-weight controls and weight-matched, obese controls. Furthermore, Roux-en-Y gastric bypass abolished the normal, meal-related fluctuations and diurnal rhythm of plasma ghrelin levels. These results do not enable a straightforward interpretation of the relationship between levels of ghrelin and weight loss. The increased plasma levels of ghrelin in the diet group would be expected to induce an increase in appetite and weight gain, rather than weight loss. Whether the reduced plasma levels of ghrelin observed after Roux-en-Y gastric bypass resulted from reduced contact between gastric mucosal mass and food, or contributed to the reduction in weight after surgery, is unclear. The important influence of residual gastric mass on postoperative ghrelin levels is illustrated by the fact that ghrelin levels do not significantly change in patients after laparoscopic adjustable gastric banding.⁸⁸

Other alterations that occur in levels of gut peptides and hormones after bariatric surgery may also contribute to weight loss. Le Roux *et al.* evaluated the effect of the Roux-en-Y gastric bypass procedure on levels of various enteric peptide hormones, including ghrelin, glucagon-like-peptide 1 and peptide YY. In line with results from the study by Cummings *et al.*, Le Roux *et al.* reported that levels of ghrelin were typically lower in patients after Roux-en-Y gastric bypass than they were before surgery. High postoperative levels of glucagon-like-peptide 1 and peptide YY were associated with increased weight loss.⁸⁹ How changes in levels of these hormones that occur after bariatric surgery alter signaling pathways to control body weight is not yet known.

Of note, although findings from several studies suggest that levels of ghrelin and other hormones, such as glucagon-like-peptide 1 or peptide YY, are altered by diet or surgery-induced weight loss and might have implications for the treatment of obesity,⁸⁹ these studies cannot conclusively differentiate association from causation. Experimental studies that involve the administration of antagonists and robust clinical trials are necessary to explore the role of these substances further in the regulation of weight loss. Development of small-molecule ghrelin antagonists for human studies will enable such mechanistic studies to be conducted in the future.

Conclusions

The modulation of ghrelin and its receptors will produce a new therapeutic armamentarium with potential therapeutic benefits in multiple systems. Ghrelin agonists may be effective for the treatment of gastrointestinal motility disorders, such as gastroparesis and postoperative ileus. Ghrelin acts directly on pancreatic islet cells to decrease insulin secretion during fasting and, in most models, increases levels of insulin after feeding. Ghrelin antagonists, therefore, have the potential to improve glycemic control, suppress appetite and induce weight loss. Glycemic control may also be improved by the administration of GOAT inhibitors, to prevent the generation of active ghrelin. Gastric capacity and emptying are unlikely to be markedly altered by ghrelin antagonists. The ability of ghrelin antagonists to induce weight loss should, therefore, be tested in clinical trials on individuals with obesity and the metabolic syndrome.

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References

1. Asakawa A, et al. Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motilin. *Gastroenterology*. 2001; 120:337–345. [PubMed: 11159873]

2. Kojima M, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*. 1999; 402:656–660. [PubMed: 10604470]
3. Howard AD, et al. A receptor in pituitary and hypothalamus that functions in growth hormone release. *Science*. 1996; 273:974–977. [PubMed: 8688086]
4. Bowers CY, et al. Structure–activity relationships of a synthetic pentapeptide that specifically releases growth hormone *in vitro*. *Endocrinology*. 1980; 106:663–667. [PubMed: 7353536]
5. Wren AM, et al. The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. *Endocrinology*. 2000; 141:4325–4328. [PubMed: 11089570]
6. Kim SW, et al. Ghrelin stimulates proliferation and differentiation and inhibits apoptosis in osteoblastic MC3T3-E1 cells. *Bone*. 2005; 37:359–369. [PubMed: 15978880]
7. Nagaya N, et al. Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. *Am J Physiol Regul Integr Comp Physiol*. 2001; 280:R1483–R1487. [PubMed: 11294772]
8. Eisenstein J, Greenberg A. Ghrelin: update. *Nutr Rev*. 2003; 61:101–104. [PubMed: 12723642]
9. Nass R, et al. Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: a randomized trial. *Ann Intern Med*. 2008; 149:601–611. [PubMed: 18981485]
10. Date Y, et al. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology*. 2000; 141:4255–4261. [PubMed: 11089560]
11. Lu S, et al. Immunocytochemical observation of ghrelin-containing neurons in the rat arcuate nucleus. *Neurosci Lett*. 2002; 321:157–160. [PubMed: 11880196]
12. Cowley MA, et al. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. *Neuron*. 2003; 37:649–661. [PubMed: 12597862]
13. Papotti M, et al. Growth hormone secretagogue binding sites in peripheral human tissues. *J Clin Endocrinol Metab*. 2000; 85:3803–3807. [PubMed: 11061542]
14. Banks WA, Tschoop M, Robinson SM, Heiman ML. Extent and direction of ghrelin transport across the blood–brain barrier is determined by its unique primary structure. *J Pharmacol Exp Ther*. 2002; 302:822–827. [PubMed: 12130749]
15. Date Y, et al. The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats. *Gastroenterology*. 2002; 123:1120–1128. [PubMed: 12360474]
16. Takeno R, et al. Intravenous administration of ghrelin stimulates growth hormone secretion in vagotomized patients as well as normal subjects. *Eur J Endocrinol*. 2004; 151:447–450. [PubMed: 15476443]
17. Kanamoto N, et al. Genomic structure and characterization of the 5′-flanking region of the human ghrelin gene. *Endocrinology*. 2004; 145:4144–4153. [PubMed: 15142980]
18. Gardiner J, Bloom S. Ghrelin gets its GOAT. *Cell Metab*. 2008; 7:193–194. [PubMed: 18316023]
19. Pemberton C, Wimalasena P, Yandle T, Soule S, Richards M. C-terminal pro-ghrelin peptides are present in the human circulation. *Biochem Biophys Res Commun*. 2003; 310:567–573. [PubMed: 14521948]
20. Zhang JV, et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. *Science*. 2005; 310:996–999. [PubMed: 16284174]
21. Gourcerol G, Tache Y. Obestatin—a ghrelin-associated peptide that does not hold its promise to suppress food intake and motility. *Neurogastroenterol Motil*. 2007; 19:161–165. [PubMed: 17300284]
22. Bang AS, Soule SG, Yandle TG, Richards AM, Pemberton CJ. Characterisation of proghrelin peptides in mammalian tissue and plasma. *J Endocrinol*. 2007; 192:313–323. [PubMed: 17283231]
23. Hosoda H, Kojima M, Mizushima T, Shimizu S, Kangawa K. Structural divergence of human ghrelin. Identification of multiple ghrelin-derived molecules produced by post-translational processing. *J Biol Chem*. 2003; 278:64–70. [PubMed: 12414809]
24. Toshinai K, et al. Des-acyl ghrelin induces food intake by a mechanism independent of the growth hormone secretagogue receptor. *Endocrinology*. 2006; 147:2306–2314. [PubMed: 16484324]

25. Qader SS, Hakanson R, Rehfeld JF, Lundquist I, Salehi A. Proghrelin-derived peptides influence the secretion of insulin, glucagon, pancreatic polypeptide and somatostatin: a study on isolated islets from mouse and rat pancreas. *Regul Pept.* 2008; 146:230–237. [PubMed: 17942170]
26. Thompson NM, et al. Ghrelin and des-octanoyl ghrelin promote adipogenesis directly *in vivo* by a mechanism independent of the type 1a growth hormone secretagogue receptor. *Endocrinology.* 2004; 145:234–242. [PubMed: 14551228]
27. Asakawa A, et al. Stomach regulates energy balance via acylated ghrelin and desacyl ghrelin. *Gut.* 2005; 54:18–24. [PubMed: 15591499]
28. Granata R, et al. Acylated and unacylated ghrelin promote proliferation and inhibit apoptosis of pancreatic beta-cells and human islets: involvement of 3', 5'-cyclic adenosine monophosphate/protein kinase A, extracellular signal-regulated kinase 1/2, and phosphatidylinositol 3-kinase/Akt signaling. *Endocrinology.* 2007; 148:512–529. [PubMed: 17068144]
29. Yang J, Brown MS, Liang G, Grishin NV, Goldstein JL. Identification of the acyltransferase that octanoylates ghrelin, an appetite-stimulating peptide hormone. *Cell.* 2008; 132:387–396. [PubMed: 18267071]
30. Gualillo O, Lago F, Dieguez C. Introducing GOAT: a target for obesity and anti-diabetic drugs? *Trends Pharmacol Sci.* 2008; 29:398–401. [PubMed: 18606462]
31. Tschöp M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. *Nature.* 2000; 407:908–913. [PubMed: 11057670]
32. Sanchez J, Oliver P, Palou A, Pico C. The inhibition of gastric ghrelin production by food intake in rats is dependent on the type of macronutrient. *Endocrinology.* 2004; 145:5049–5055. [PubMed: 15284203]
33. de la Cour CD, Norlen P, Hakanson R. Secretion of ghrelin from rat stomach ghrelin cells in response to local microinfusion of candidate messenger compounds: a microdialysis study. *Regul Pept.* 2007; 143:118–126. [PubMed: 17573135]
34. Bellone S, et al. Ghrelin secretion in childhood is refractory to the inhibitory effect of feeding. *J Clin Endocrinol Metab.* 2004; 89:1662–1665. [PubMed: 15070928]
35. Shiiya T, et al. Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. *J Clin Endocrinol Metab.* 2002; 87:240–244. [PubMed: 11788653]
36. Pekic S, et al. Plasma ghrelin levels of gastrectomized and vagotomized patients are not affected by glucose administration. *Clin Endocrinol (Oxf).* 2006; 64:684–688. [PubMed: 16712672]
37. Kim MS, et al. Changes in ghrelin and ghrelin receptor expression according to feeding status. *Neuroreport.* 2003; 14:1317–1320. [PubMed: 12876464]
38. Wren AM, et al. Ghrelin causes hyperphagia and obesity in rats. *Diabetes.* 2001; 50:2540–2547. [PubMed: 11679432]
39. Inui A. Ghrelin: an orexigenic and somatotrophic signal from the stomach. *Nat Rev Neurosci.* 2001; 2:551–560. [PubMed: 11483998]
40. Wren AM, et al. Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab.* 2001; 86:5992–5995. [PubMed: 11739476]
41. Smith RG, et al. Peptidomimetic regulation of growth hormone secretion. *Endocr Rev.* 1997; 18:621–645. [PubMed: 9331545]
42. Horvath TL, Diano S, Sotonyi P, Heiman M, Tschöp M. Minireview: ghrelin and the regulation of energy balance—a hypothalamic perspective. *Endocrinology.* 2001; 142:4163–4169. [PubMed: 11564668]
43. Gil-Campos M, Canete R, Gil A. Hormones regulating lipid metabolism and plasma lipids in childhood obesity. *Int J Obes Relat Metab Disord.* 2004; 28 (suppl 3):S75–S80. [PubMed: 15543224]
44. Haqq AM, et al. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader–Willi syndrome. *J Clin Endocrinol Metab.* 2003; 88:174–178. [PubMed: 12519848]
45. Asakawa A, et al. Antagonism of ghrelin receptor reduces food intake and body weight gain in mice. *Gut.* 2003; 52:947–952. [PubMed: 12801949]
46. Strassburg S, et al. Long-term effects of ghrelin and ghrelin receptor agonists on energy balance in rats. *Am J Physiol Endocrinol Metab.* 2008; 295:E78–E84. [PubMed: 18460598]

47. Gil-Campos M, Aguilera CM, Canete R, Gil A. Ghrelin: a hormone regulating food intake and energy homeostasis. *Br J Nutr.* 2006; 96:201–226. [PubMed: 16923214]
48. Olszewski PK, Schioth HB, Levine AS. Ghrelin in the CNS: from hunger to a rewarding and memorable meal? *Brain Res Rev.* 2008; 58:160–170. [PubMed: 18308399]
49. Venkova K, Greenwood-Van Meerveld B. Application of ghrelin to gastrointestinal diseases. *Curr Opin Investig Drugs.* 2008; 9:1103–1107.
50. Peeters TL. Potential of ghrelin as a therapeutic approach for gastrointestinal motility disorders. *Curr Opin Pharmacol.* 2006; 6:553–558. [PubMed: 17011824]
51. Lasseter KC, et al. Ghrelin agonist (TZIP-101): safety, pharmacokinetics and pharmacodynamic evaluation in healthy volunteers: a phase I, first-in-human study. *J Clin Pharmacol.* 2008; 48:193–202. [PubMed: 18199894]
52. Fraser GL, Hoveyda HR, Tannenbaum GS. Pharmacological demarcation of the growth hormone, gut motility and feeding effects of ghrelin using a novel ghrelin receptor agonist. *Endocrinology.* 2008; 149:6280–6288. [PubMed: 18719021]
53. Tranzyme® Pharma [online]. 2009. <http://www.tranzyme.com>
54. Delhanty PJ, et al. Ghrelin and its unacylated isoform stimulate the growth of adrenocortical tumor cells via an anti-apoptotic pathway. *Am J Physiol Endocrinol Metab.* 2007; 293:E302–E309. [PubMed: 17405826]
55. Frasca F, et al. The role of insulin receptors and IGF-I receptors in cancer and other diseases. *Arch Physiol Biochem.* 2008; 114:23–37. [PubMed: 18465356]
56. Koo GC, et al. Immune enhancing effect of a growth hormone secretagogue. *J Immunol.* 2001; 166:4195–4201. [PubMed: 11238671]
57. Katargari SA, Milousis A, Pagonopoulou O, Asimakopoulos B, Nikolettos NK. Ghrelin in pathological conditions. *Endocr J.* 2008; 55:439–453. [PubMed: 18323676]
58. Cremonini F, et al. Obesity does not increase effects of synthetic ghrelin on human gastric motor functions. *Gastroenterology.* 2006; 131:1431–1439. [PubMed: 17101319]
59. Sanger GJ. Motilin, ghrelin and related neuropeptides as targets for the treatment of GI diseases. *Drug Discov Today.* 2008; 13:234–239. [PubMed: 18342799]
60. Tack J, et al. Influence of ghrelin on interdigestive gastrointestinal motility in humans. *Gut.* 2006; 55:327–333. [PubMed: 16216827]
61. Peeters TL. Central and peripheral mechanisms by which ghrelin regulates gut motility. *J Physiol Pharmacol.* 2003; 54:95–103. [PubMed: 15075452]
62. Qiu WC, Wang ZG, Wang WG, Yan J, Zheng Q. Gastric motor effects of ghrelin and growth hormone releasing peptide 6 in diabetic mice with gastroparesis. *World J Gastroenterol.* 2008; 14:1419–1424. [PubMed: 18322959]
63. Murray CD, et al. Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study. *Gut.* 2005; 54:1693–1698. [PubMed: 16085693]
64. Tack J, et al. Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis. *Aliment Pharmacol Ther.* 2005; 22:847–853. [PubMed: 16225494]
65. Binn M, et al. Ghrelin gastroduodenal action in patients with neurogenic gastroparesis. *Peptides.* 2006; 27:1603–1606. [PubMed: 16426704]
66. Levin F, et al. Ghrelin stimulates gastric emptying and hunger in normal-weight humans. *J Clin Endocrinol Metab.* 2006; 91:3296–3302. [PubMed: 16772353]
67. Esler WP, et al. Small-molecule ghrelin receptor antagonists improve glucose tolerance, suppress appetite, and promote weight loss. *Endocrinology.* 2007; 148:5175–5185. [PubMed: 17656463]
68. Adeghate E, Ponery AS. Ghrelin stimulates insulin secretion from the pancreas of normal and diabetic rats. *J Neuroendocrinol.* 2002; 14:555–560. [PubMed: 12121492]
69. Volante M, et al. Expression of ghrelin and of the GH secretagogue receptor by pancreatic islet cells and related endocrine tumors. *J Clin Endocrinol Metab.* 2002; 87:1300–1308. [PubMed: 11889202]
70. Dezaki K, et al. Endogenous ghrelin in pancreatic islets restricts insulin release by attenuating Ca^{2+} signaling in β -cells: implication in the glycemic control in rodents. *Diabetes.* 2004; 53:3142–3151. [PubMed: 15561944]

71. Sun Y, Wang P, Zheng H, Smith RG. Ghrelin stimulation of growth hormone release and appetite is mediated through the growth hormone secretagogue receptor. *Proc Natl Acad Sci USA*. 2004; 101:4679–4684. [PubMed: 15070777]
72. Damjanovic SS, et al. Acute effects of ghrelin on insulin secretion and glucose disposal rate in gastrectomized patients. *J Clin Endocrinol Metab*. 2006; 91:2574–2581. [PubMed: 16621911]
73. Chapman IM, et al. Stimulation of the growth hormone (GH)-insulin-like growth factor I axis by daily oral administration of a GH secretagogue (MK-677) in healthy elderly subjects. *J Clin Endocrinol Metab*. 1996; 81:4249–4257. [PubMed: 8954023]
74. Sun Y, Asnicar M, Saha PK, Chan L, Smith RG. Ablation of ghrelin improves the diabetic but not obese phenotype of ob/ob mice. *Cell Metab*. 2006; 3:379–386. [PubMed: 16679295]
75. Takahashi H, et al. Ghrelin differentially modulates glucose-induced insulin secretion according to feeding status in sheep. *J Endocrinol*. 2007; 194:621–625. [PubMed: 17761901]
76. Dezaki K, et al. Blockade of pancreatic islet-derived ghrelin enhances insulin secretion to prevent high-fat diet-induced glucose intolerance. *Diabetes*. 2006; 55:3486–3493. [PubMed: 17130496]
77. Broglio F, et al. Non-acylated ghrelin counteracts the metabolic but not the neuroendocrine response to acylated ghrelin in humans. *J Clin Endocrinol Metab*. 2004; 89:3062–3065. [PubMed: 15181099]
78. Gauna C, et al. Ghrelin stimulates, whereas des-octanoyl ghrelin inhibits, glucose output by primary hepatocytes. *J Clin Endocrinol Metab*. 2005; 90:1055–1060. [PubMed: 15536157]
79. Zhang Y, et al. Ghrelin inhibits cell apoptosis in pancreatic beta cell line HIT-T15 via mitogen-activated protein kinase/phosphoinositide 3-kinase pathways. *Toxicology*. 2007; 237:194–202. [PubMed: 17602820]
80. Sun Y, Ahmed S, Smith RG. Deletion of ghrelin impairs neither growth nor appetite. *Mol Cell Biol*. 2003; 23:7973–7981. [PubMed: 14585959]
81. Sun Y, Butte NF, Garcia JM, Smith RG. Characterization of adult ghrelin and ghrelin receptor knockout mice under positive and negative energy balance. *Endocrinology*. 2008; 149:843–850. [PubMed: 18006636]
82. Deitel M, Crosby RD, Gagner M. The First International Consensus Summit for Sleeve Gastrectomy (SG), New York City, October 25–27, 2007. *Obes Surg*. 2008; 18:487–496. [PubMed: 18357494]
83. Schauer, PR.; Schirmer, BD. Schwartz's Principles of Surgery. 8. Brunicaudi, F., editor. McGraw-Hill Health Professions Division; New York: 2005.
84. O'Brien PE, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med*. 2006; 144:625–633. [PubMed: 16670131]
85. Sjostrom L, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004; 351:2683–2693. [PubMed: 15616203]
86. Sjostrom L, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007; 357:741–752. [PubMed: 17715408]
87. Cummings DE, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med*. 2002; 346:1623–1630. [PubMed: 12023994]
88. Shak J, et al. The effect of laparoscopic gastric banding surgery on plasma levels of appetite-control, insulinotropic, and digestive hormones. *Obes Surg*. 2008; 18:1089–1096. [PubMed: 18408980]
89. le Roux CW, et al. Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. *Ann Surg*. 2007; 246:780–785. [PubMed: 17968169]
90. Kojima M, Hosoda H, Matsuo H, Kangawa K. Ghrelin: discovery of the natural endogenous ligand for the growth hormone secretagogue receptor. *Trends Endocrinol Metab*. 2001; 12:118–122. [PubMed: 11306336]

Key points

- Serum levels of ghrelin are reduced in obese individuals
- Whether the reduced ghrelin levels observed in patients after bypass bariatric surgery are a cause of weight loss or a consequence of the procedure is unclear
- Ghrelin agonists accelerate gastric emptying and could potentially be used to treat gastroparesis and postoperative ileus
- Ghrelin antagonists are unlikely to delay gastric emptying or to cause upper gastrointestinal symptoms
- Small-molecule ghrelin-receptor antagonists improve glucose tolerance, suppress appetite and promote weight loss in animals; their safety and efficacy in humans should be tested in clinical trials

Review criteria

PubMed was searched in October 2008 using the terms “ghrelin”, “obesity”, “metabolic syndrome”, “small-molecule ghrelin-receptor antagonists” and “glucose regulation”, both alone and in combination. English-language papers and full reports published since 1999 and reviews published until 2008 were included with a focus on results from studies in humans and experimental animals.

Figure 1.

Ghrelin affects multiple systems. Ghrelin is secreted mainly by the stomach, but has effects in multiple areas, including the CNS, the immune system, the adrenal gland and the cardiovascular system. Ghrelin can also affect the proliferation of osteoblasts and neoplastic cells. Abbreviations: CNS, central nervous system; GH, growth hormone.

Figure 2. Effects of ghrelin on digestive functions of the upper gastrointestinal tract. Ghrelin can affect digestive functions by vagal signaling, directly within the enteric nervous system or within the CNS after crossing the blood-brain barrier. Ghrelin stimulates gastric and small-intestinal motor functions and inhibits insulin release from the pancreas. Abbreviations: CNS, central nervous system; MMC, migrating motor complexes.

Figure 3.

Effect of ghrelin and ghrelin antagonists on insulin secretion. **a** | Ghrelin decreased and a ghrelin antagonist ([D-Lys³]-GHRP-6) increased plasma levels of insulin. **b** | In gastrectomized rats, the ghrelin antagonist still increased insulin, which suggests a direct effect on pancreatic secretion of insulin. Copyright © 2006 American Diabetes Association From *Diabetes*[®], Vol. 55, 2006; 3486–3493. Reprinted with permission from The American Diabetes Association.

Table 1

Clinical studies of exogenous ghrelin effects on upper gastrointestinal function

Reference	Participants	Total ghrelin dose administered	Estimated total ghrelin dose (pmol/kg)	Mode of administration	Effect on gastric emptying	Effect on gastric volumes and/or tone	Effect on MMCs	Effect on postprandial symptoms
Wren <i>et al.</i> (2001) ⁴⁰	9 volunteers	5 pmol · kg ⁻¹ /min	1350	Infusion over 270 min	No effect	ND	ND	ND
Cremolini <i>et al.</i> (2006) ⁵⁸	38 (normal weight + obese)	100 pmol/kg (0.33 µg/kg)	100	Bolus	No effect	Trend to reduced fasting and postprandial volumes	ND	No effect
Tack <i>et al.</i> (2006) ⁶⁰	9 healthy volunteers	40 µg	170 ^a	Infusion over 30 min	ND	Prolonged increase in gastric tone	Premature phase III	ND
Tack <i>et al.</i> (2005) ⁶⁴	6 with idiopathic gastroparesis	40 µg	170 ^a	Infusion over 30 min	Increased emptying of liquids	ND	ND	Improved postprandial fullness and pain
Murray <i>et al.</i> (2005) ⁶³	10 with diabetes	5 pmol · kg ⁻¹ /min	600	Infusion over 120 min	Increased GER in 7 of 10 patients	ND	ND	No difference in bloating, hunger, nausea
Binn <i>et al.</i> (2005) ⁶⁵	6 with neurogenic gastroparesis	1 µg/kg (plus re-treatment with 4 µg/kg for patients who did not respond to initial dose)	303 (or 1212 with re-treatment dose)	Bolus	Increased in 4 of 6 patients Increased in another 2 patients with re-treatment	ND	ND	ND
Levin <i>et al.</i> (2006) ⁶⁶	8 healthy volunteers + 6 GH-deficient	10 pmol · kg ⁻¹ /min	1800	Infusion over 180 min	Increased emptying of solids	ND	ND	ND

^aBased on the molecular weight of octanoylated ghrelin (3,371 kDa).⁹⁰ Assuming patients had a mean weight of 70 kg.

Abbreviations: GER, gastric emptying rate; GH, growth hormone; ND, not done; MMC, migrating motor complexes.