

Ghrelin, an endogenous growth hormone secretagogue with diverse endocrine and nonendocrine effects

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Circulating ghrelin, the natural ligand of GHS-R 1a, is synthesized primarily in the stomach in mammals. The distribution of these receptors is consistent with the role of ghrelin in promoting secretion of GH; receptors are highly expressed in the hypothalamus and pituitary gland and are also distributed in other central and peripheral tissue sites. In addition to strong GH-releasing activity, ghrelin has other actions, including stimulation of lactotroph and corticotroph function, stimulation of appetite, regulation of energy homeostasis, stimulation of gastric motility and gastric acid secretion, regulation of insulin secretion and glucose metabolism, cardiovascular effects, and antiproliferative activity. These properties make ghrelin a candidate for future diagnostic and clinical applications.

In mammals, secretion of GH from the adenohypophysis is regulated by 2 hypothalamic hormones with antagonistic actions: a stimulatory GHRH that is produced in the arcuate nucleus and an inhibitory hormone, somatostatin, synthesized in the paraventricular nucleus.¹ Both hormones are transported from the hypothalamus to target cells in the pituitary gland via the hypothalamo-hypophyseal portal system in the median eminence. Alternation in secretion of GHRH and somatostatin is responsible for the pulsatile pattern of GH release.^{2,3} Measurement of GHRH and somatostatin in hypophyseal-portal blood in humans and other animals reveals that the episodic pattern of GHRH and somatostatin secretion does not fully account for all pulses of GH secretion.⁴ The amplitude and frequency of GH secretory pulses are regulated by a complex array of external and internal stimuli, including body composition, age, sleep, gender, disease status, menstrual cycle phase, genetic background, and nutritional status.⁵⁻⁷

The discovery of ghrelin, the natural ligand of GHS-R 1a, was an important advance in the understanding of regulation of GH secretion.⁸ Ghrelin has been isolated from tissues of the stomach, where its expression is higher than in any other tissue.⁸ The site of ghrelin production and its molecular structure, which contains an octanoyl group, were initially surprising to investigators.

Apart from its role in stimulating pituitary release of GH, ghrelin has many other actions. The discovery of ghrelin and its various physiologic actions opened new avenues of research, not only in the field of neuroendocrinology, but also in the areas of gastroenterology, immunology, oncology, cardiology, reproduction, cell proliferation and growth, energy homeostasis, and energy balance. In this overview, we summarize recent findings on the physiologic effects of ghrelin in several mammalian species and describe future diagnostic and clinical applications.

Growth Hormone

Growth hormone, a 191-amino acid, single-chain polypeptide, is synthesized, stored, and secreted by somatotroph cells in the adenohypophysis.⁹ The effects of GH on growth and metabolic functions are mediated through the GH receptor. Growth hormone forms complexes with 2 peripheral GH receptor components, leading to dimerization of the receptor, an event that is necessary for subsequent GH signaling. Growth hormone receptor dimerization elicits an intracellular phosphorylation cascade involving the JAK-STAT (Janus kinase signal transducers and activators of transcription) pathway.¹⁰

The liver contains abundant GH receptors, and several other peripheral tissues, including muscle and fat, express modest amounts of GH receptors.¹¹ In contrast to most other pituitary hormones, the action of GH is not confined to a single target tissue and the hormone has both slow anabolic and rapid catabolic activities.¹² The catabolic effects are exerted via direct interaction with target cells, resulting in enhanced lipolysis in fat cells, and restriction of glucose transport across the cell membrane, caused by anti-insulin activity.¹²⁻¹⁴ The anabolic effects (ie, growth and cell proliferation) of GH are exerted indirectly, mainly mediated by growth factors known as IGFs or somatomedins.¹⁵ The liver is the primary source of circulating IGFs. Growth hormone also promotes the production of IGFs in peripheral tissues (eg, muscle, bone, cartilage, kidney, and skin), where they appear to have autocrine and paracrine effects.¹⁵

Insulin-like growth factors have approximately 50% amino acid sequence similarity with insulin.¹⁶ In

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GHS-R 1a	GH secretagogue receptor type 1a
GH	Growth hormone
GHRH	GH-releasing hormone
IGF	Insulin-like growth factor
GHRP-6	GH-releasing peptide-6
GHS	GH secretagogue
PRL	Prolactin
GHS-R	GHS receptor

contrast to circulating insulin, IGFs are bound to plasma proteins, which prolongs their half-life and contributes to their long-term growth-promoting effects. Circulating IGFs are important determinants of body size because they stimulate protein synthesis, chondrogenesis, and body growth. Insulin-like growth factor-1 has an inhibitory effect on GH secretion, most likely by stimulating the release of somatostatin and by a directly inhibitory influence at the level of the pituitary gland.¹⁷ Additionally, GH has a negative feedback effect on its own production at the level of the hypothalamus.¹⁸

Synthetic Growth Hormone Secretagogues

The usual sequence of discovery in endocrinology is isolation of a hormone, cloning of its receptor, and development of analogs of the hormone for clinical use. With ghrelin, this sequence was reversed: first, analogs were synthesized, then the receptor was cloned, and lastly, the natural ligand of the orphan receptor was isolated.

Briefly, in 1975, before the discovery of GHRH, the GH-releasing properties of enkephalins were reported.¹⁹ Chemical modification of the structure of met-enkephalin led to development of a highly potent GH-releasing hexapeptide, GHRP-6 [(His-D-Trp-Ala-Trp-D-Phe-Lys-NH₂)³], in 1980.²⁰ One of the most remarkable properties of GHRP-6 was the strong GH-releasing activity induced following oral administration.²¹ The hexapeptide was the basic structure from which synthetic GHSs, of either peptidergic structure such as hexarelin or nonpeptidergic structure such as MK-0677,^{22,23} were subsequently produced. Currently used synthetic GHSs are highly bioavailable and may be administered via IV, IM, intranasal, SC, oral, and transdermal routes.²⁴ Because GH is a large protein that must be administered via injection or inhalation, administration of synthetic GHSs is often preferred over administration of GH. In addition, GHSs induce a more physiologic pulsatile pattern of GH release.^{24,25} For example, a single orally administered dose of MK-0677 increases mean 24-hour plasma GH concentrations.^{21,23,26}

The synthetic GHSs have potent GH-releasing activity in several species, including humans, mice, rats, swine, goats, cows, and dogs.²⁷⁻²⁹ In humans, nearly all synthetic GHSs induce the release of more GH than does GHRH.²⁴ However, the hormone-releasing action of synthetic GHSs is not always specific.²⁴ In humans, synthetic GHSs such as GHRP-6 also have a stimulatory effect on the secretion of PRL, ACTH, and cortisol.^{24,30,31} Newer selective GHSs, such as ipamorelin, do not have ACTH- or PRL-releasing actions.^{32,33}

Interest in GHSs faded after the isolation and characterization of GHRH in 1982,^{34,35} but was later revived when it was discovered that GHSs operated through receptors that are different from those for GHRH.^{24,36,37} Growth hormone secretagogues and GHRH have strongly synergistic actions, which indicates that synthetic GHSs are not physiologic surrogates of GHRH.³⁸ In 1996, GHS-R, a G-protein-coupled 7-transmembrane receptor, was identified.³⁹ This receptor has been cloned from cells of the pituitary gland in humans^{36,40} and rats.⁴¹

Two types of GHS-Rs, which are presumably the result of alternate processing of pre-mRNA, have been identified and designated as receptors 1a and 1b.^{21,36} Human GHS-R 1a shares 96% and 93% sequence identity with rat and pig receptors, respectively. The existence of this receptor can be traced to animals in the pre-Cambrian era because amino acid sequences highly similar to those in the human GHS-R 1a have been detected in teleost fish.⁴² These observations indicate that the GHS-R 1a is highly conserved across species and likely has an essential biological function. This receptor is largely confined to somatotroph cells in the pituitary gland and to several hypothalamic nuclei (eg, the supraoptic, arcuate, and paraventricular nuclei) in humans and rats.^{21,36,37,43} Messenger RNA encoding GHS-R 1a has been detected in the pituitary gland, indicating that GHSs can act directly on somatotrophs to stimulate GH release. This is in accordance with an earlier observation⁴⁴ that GHSs are able to directly stimulate GH release from rat pituitary cells in vitro. The hypothalamic localization of the GHS-R 1a, especially in the supraoptic and paraventricular nuclei, supports the notion that GHSs may also indirectly regulate GH release by interacting with GHRH-producing neurons, somatostatin-producing neurons, or both, in the hypothalamus.⁴⁵ The GHS-R 1a is also expressed in other areas of the brain and certain peripheral tissues,⁴⁶ indicating that GHSs may also be involved in other physiologic functions.^{37,47} The importance of the widespread expression of GHS-R 1b in endocrine and nonendocrine tissues has not been determined.^{36,48}

The GHS-Rs are distinct from the GHRH receptor.^{36,37,40} Although binding of GHRH to the GHRH receptor increases cAMP in somatotroph cells and stimulates GH release via activation of the kinase A pathway, binding of ghrelin and synthetic GHSs to the GHS-R 1a activates the phospholipase C signaling pathway, leading to an increase in inositol triphosphate and protein kinase C activation, followed in turn by release of calcium from intracellular stores.³⁹ Unlike GHS-R 1a, GHS-R 1b does not bind ghrelin or synthetic GHSs, and its function awaits clarification.^{36,40,48}

Ghrelin

The 1999 discovery of the endogenous or natural ligand of the GHS-R, termed ghrelin (*ghre* is the proto-Indo-European root of the word grow, and *relin* indicates release), provided a new dimension to GH research.⁸ Ghrelin causes release of GH in vitro and in vivo. The 28-amino acid peptide was isolated from the stomach, where its expression is higher than in any other tissue.⁸ Although this source may initially seem strange, it should be remembered that most circulating somatostatin is synthesized in the intestines and pancreas and that GHRH was first isolated not from the hypothalamus but from a pancreatic tumor.⁴⁹ Thus, the 3 neurohormones (ie, somatostatin, GHRH, and ghrelin) responsible for regulation of GH secretion are highly expressed in gastrointestinal tissues.

In humans, rats, and domestic animals, expression of ghrelin mRNA and the ghrelin peptide is primarily detected in the enteroendocrine or X-A-like cells of the fundic glands in the stomach,^{27,50} which have been

renamed Ghr-cells. The cells containing ghrelin do not communicate with the lumen of the fundic gland but, like all enteroendocrine cells, are positioned adjacent to capillaries, indicating that their primary action is secretion of hormone into plasma and not into the intestinal lumen.⁵¹

The degree of structural heterogeneity of ghrelin among species appears to be minor, suggesting that there is little functional heterogeneity. Such preservation of structure also reflects the physiologic relevance of the peptide.^{49,50} For example, human and rat ghrelin differ in only 2 amino acids (Table 1).⁵² Alternative splicing of mRNA segments encoding ghrelin yields 2 different peptides, ghrelin and des-Gln14-ghrelin.⁵³ The latter is homologous with ghrelin except for the absence of a single glutamine residue. Des-Gln14-ghrelin is expressed in the stomach in low quantities,⁴⁷ but like ghrelin, it increases the intracellular concentration of calcium in cells that express the GHS-R 1a and increases plasma GH concentrations.^{8,53}

Before being secreted, *n*-octanoic acid is added to the third serine residue of ghrelin and des-Gln14-ghrelin (Figure 1).⁵² This acylation step, unique to mammalian species, is essential for binding to and activating the GHS-R 1a⁵⁴ and hence for the peptide's GH-releasing action. Acylation is most likely also necessary for the other endocrine actions of the ghrelin molecule.^{47,55} Addition of the *n*-octanoyl group confers a hydrophobic property to the N terminus of the peptide. It has been suggested that the octanoylation of ghrelin is critical to the peptide's ability to cross the blood-brain barrier. It may also facilitate distribution of the peptide in the brain, although there are presently no data to support this speculation.⁵⁶ Nonacylated ghrelin is found in far greater quantities in human serum than acylated ghrelin, but appears to lack endocrine activity. However, this peptide does have certain nonendocrine cardiovascular and antiproliferative effects, which are likely mediated by binding to a novel and as-yet unidentified GHS-R subtype.⁵⁷ Nonacylated ghrelin inhibits proliferation of human prostate cancer cell lines and neoplastic cell growth in thyroid, breast, and lung tumors. Cardioprotective and negative inotropic effects have also been described.^{51,57}

Lower concentrations of ghrelin have been detected in various other tissues, including the intestines,⁵¹ pituitary gland,⁵⁸ hypothalamus,^{8,51} kidney,⁵⁹ placenta,⁶⁰ heart,⁴⁹ testis,⁶¹ thyroid gland,⁶² pancreas,⁶³ lung,⁶⁴ ovary,⁶⁵ immune system,⁶⁶ and neoplastic tissue.⁴⁶ The physiologic importance of ghrelin as

a paracrine factor in these tissues is under investigation, but an endocrine role for non-stomach-derived ghrelin is thought to be unlikely. Removal of the stomach in humans and rats decreases the plasma concentration of ghrelin by approximately 65% and 80%, respectively.^{51,67} However, plasma ghrelin concentrations gradually increase after gastrectomy.⁶⁸ These findings indicate that the stomach is the major source of circulating ghrelin but that other tissues may increase secretion of ghrelin in a compensatory manner.⁶⁹

Endocrine Effects of Ghrelin

Ghrelin has pronounced, dose-related GH-releasing actions that are more marked in humans than in other mammals.^{8,21,27-29,31,51,70-73} The GH-releasing activity of ghrelin is greater in vivo than in vitro because ghrelin and GHRH act synergistically, consistent with the fact that their actions are at least partially mediated via different mechanisms.^{21,74} Nevertheless, GHRH activity is required for full expression of ghrelin's GH-releasing activity.^{21,74} The GH response to ghrelin is partially inhibited by GHRH receptor antagonists and disruption of communication between the hypothalamus and pituitary gland,^{75,76} supporting the assumption that the effect of ghrelin on GH secretion is primarily mediated by GHRH-secreting neurons at the level of the hypothalamus.^{21,74,76,77}

In anesthetized rats, ghrelin administered IV stimulates GH release without affecting secretion of other adenohypophyseal hormones.⁸ Also, in cultured rat pituitary cells, ghrelin stimulates GH release in a dose-dependent manner without affecting the release of other pituitary hormones, even at high concentrations.⁸ However, in healthy humans, ghrelin is not specific for GH release because it also has stimulatory effects on lactotroph and corticotroph cells.^{31,72,78,79} The effect of ghrelin on PRL secretion is independent of gender and age and likely results from direct stimulation of somatomammotrophs.^{72,78,80,81} In dogs^{28,29} and rats,⁸ synthetic GHSs do not stimulate PRL release. This species-related difference may be explained by differences in the number of somatomammotrophs in various species, with humans having a high proportion of those cells.^{32,82} The mechanism by which ghrelin stimulates the pituitary-adrenocortical axis is still unknown, but it is thought to be mediated via the hypothalamus because the stimulatory effect is lost after sectioning of the pituitary stalk.⁸³ Ghrelin may also interact with hypothalamic peptides that control ACTH release, probably via arginine vasopressin.^{55,84,85}

Table 1—Primary structure of ghrelin in domestic mammalian species.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Species
G	S	S	F	L	S	P	E	H	Q	R	V	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R	Human
G	S	S	F	L	S	P	E	H	Q	K	T	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R	Gerbil
G	S	S	F	L	S	P	E	H	Q	K	A	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R	Mouse
G	S	S	F	L	S	P	E	H	Q	K	A	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R	Rat
G	S	S	F	L	S	P	E	H	Q	K	L	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R	Dog
G	S	S	F	L	S	P	E	H	Q	K	V	Q	Q	R	K	E	S	K	K	P	A	A	K	L	K	P	R	Pig
G	S	S	F	L	S	P	E	H	Q	K	L	Q	Q	R	K	E	A	K	K	P	S	G	R	L	K	P	R	Cattle
G	S	S	F	L	S	P	E	H	Q	K	L	Q	Q	R	K	E	P	K	K	P	S	G	R	L	K	P	R	Sheep
G	S	S	F	L	S	P	T	Y	K	N	I	Q	Q	Q	K	D	T	R	K	P	T	A	R	L	H	R	R	Chicken

(Adapted from van der Lely et al.⁵² Reprinted with permission [copyright 2004, The Endocrine Society].)

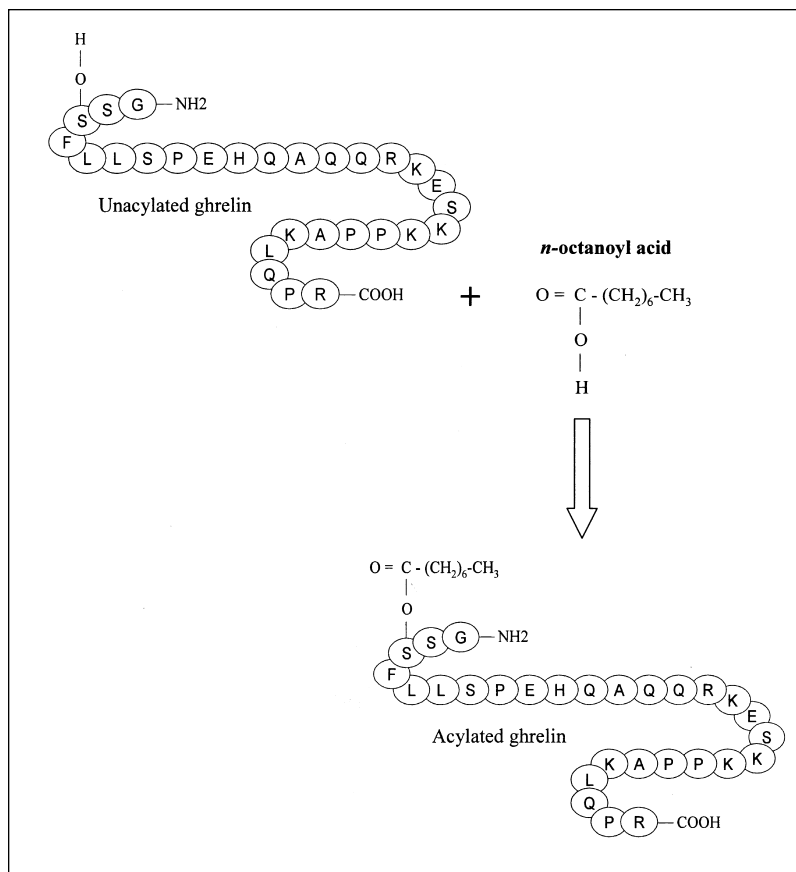


Figure 1—Illustration of acylation of the ghrelin molecule. A hydroxyl group on the serine residue at position 3 of the ghrelin molecule is octanoylated. This esterification is unique to mammals and is essential for ghrelin binding to and activating GHS-R 1a and, consequently, for the GH-releasing action of ghrelin. The other endocrine actions of ghrelin are also likely dependent on acylation of the peptide. (Adapted from van der Lely et al.⁵² Reprinted with permission [copyright 2004, The Endocrine Society].)

Orexigenic Actions and Role in Energy Homeostasis

Evidence for involvement of ghrelin in regulation of appetite was first detected in humans. Healthy human volunteers reported hunger after administration of ghrelin in a clinical study in which GH release was analyzed.⁸⁶ In rodents, ghrelin stimulates food intake and increases body weight while reducing mobilization of adipose stores.^{87–89} The effects of ghrelin on food intake are likely mediated through mechanisms other than those implicated in GH regulation, compatible with the concept of distinct GHS-R subtypes.^{87,90}

Adipocytes traditionally have been viewed as energy depots in which triglycerides are stored during feeding and that release fatty acids during fasting to provide fuel for other tissues. However, it is now known that adipose tissue has major integrative physiologic functions, including secretion of numerous proteins.^{91,92} The realization that adipose tissue has endocrine functions has important implications for our understanding of the associations between excessive body fat and pathologic states such as insulin resistance and type 2 diabetes mellitus.⁹²

An important finding that linked central regulation of metabolism to mobilization of peripheral ener-

gy stores was the discovery of the adipose hormone, leptin (from the Greek root *leptos*, meaning thin). Leptin, a peptide hormone discovered in 1994, is produced principally by white adipose tissue.⁹³ Leptin crosses the blood-brain barrier to act via receptors in the arcuate nucleus of the hypothalamus to inhibit release of orexigenic neuropeptides and stimulate release of anorexigenic neuropeptides.^{91,94} A direct relationship exists between plasma leptin concentrations and percentage body fat. Plasma leptin concentrations in humans are generally proportional to adipose mass. Decreases in leptin concentrations occur in conditions characterized by loss of adipose mass, such as anorexia nervosa, diet- or exercise-induced weight loss, or starvation. Concentrations of circulating leptin decrease rapidly within 12 hours after initiation of starvation, whereas concentrations increase in response to overfeeding. Thus, plasma leptin concentrations reflect adipose tissue mass and provide a signal that informs the CNS about the body's energy reserves.⁹¹

The similarities and complementary actions between leptin and ghrelin are intriguing. The effects of ghrelin on metabolism appear to be the opposite to those of leptin.^{47,87,95,96} Leptin reduces food intake and selectively reduces fat mass without altering lean body mass.⁹⁷ Ghrelin, in contrast, increases food intake and selectively enhances fat mass.⁸⁷

Ghrelin stimulates food intake in rodents when administered via central or peripheral routes (ie, intracerebroventricularly or SC), although the effect is more powerful after central administration.⁸⁷ There is evidence that the appetite-stimulating effects of ghrelin are mediated by secretion of 2 potent orexigenic hypothalamic hormones (neuropeptide Y and agouti-related peptide) and by inhibition of pro-opiomelanocortin and α -melanocyte-stimulating hormone.^{98–101} Furthermore, the orexigenic action of ghrelin is eliminated when the effects of neuropeptide Y and agouti-related peptide are antagonized.⁹⁹ By stimulating the release of orexigenic peptides and neurotransmitters, ghrelin mediates a novel circuit regulating energy homeostasis.^{101–105}

In humans and rats, concentrations of circulating ghrelin decrease in chronic (obesity)¹⁰⁶ and acute (caloric intake)¹⁰⁷ states of positive energy balance, whereas ghrelin concentrations increase in states of negative energy balance (eg, fasting).⁸⁷ In cattle, plasma ghrelin concentrations are low 1 hour after feeding and then return to the prefeeding concentration.²⁷ In sheep, the preprandial ghrelin surge is higher in animals fed twice daily than in animals fed 4 times daily, indicating that different feeding regimens influence ghrelin concentrations.¹⁰⁸ The preprandial increase and postpran-

dial decrease in plasma ghrelin concentrations suggest a possible role for ghrelin as a hunger signal that triggers meal initiation.¹⁰⁷ Because ghrelin is a potent stimulator of GH release, these observations are in accordance with the low plasma GH concentrations associated with obesity¹⁰⁹ and the high concentrations observed in the malnourished and fasting states.¹¹⁰

It may be concluded that nutritional state is an important determinant of plasma ghrelin concentration.¹¹¹ Ghrelin peptide reaches ghrelin receptors in the hypothalamo-pituitary region via the general circulation, where it stimulates GH release and regulates energy homeostasis. It is unclear whether ghrelin may cross the blood-brain barrier to influence the activity of these central structures.⁵² In the general circulation, ghrelin is bound to high-density lipoproteins in the serum and presumably to other proteins, such as albumin. Ghrelin may also signal the brain directly, by activating the afferent portion of the vagal nervous system as either an endocrine or a paracrine signal, at the level of the stomach. Ghrelin-responsive GHS-Rs are expressed on gastric vagal nerves, and vagotomy prevents some of the effects of ghrelin on energy balance. On the other hand, the extent and direction of ghrelin transport across the blood-brain barrier may be determined by its unique primary structure.¹¹² There is debate among scientists concerning the routes by which ghrelin in the peripheral circulation activates receptors in the CNS of different species.

Gastric Prokinetic Action

Ghrelin induces strong prokinetic activity in the stomach.^{113,114} The peptide dramatically accelerates gastric and intestinal emptying in rats, and circulating ghrelin concentrations are correlated with gastric emptying time in humans.¹¹⁵ In addition, ghrelin stimulates gastric acid secretion.¹¹⁴

In that context, structural and functional similarities exist between ghrelin and motilin.¹¹⁵ In addition to prokinetic effects on the gastrointestinal tract, both peptides have orexigenic properties¹¹⁶ and stimulatory effects on pituitary GH release.¹¹⁷ The G-protein-coupled receptors of ghrelin and motilin also have a high degree of structural homology.¹¹⁸ In contrast to ghrelin, motilin is primarily expressed in the small intestine.¹¹⁹ Motilin stimulates motor activity in the gastric antrum and proximal portion of the duodenum and plays a key role in the regulation of motility between meals.¹²⁰

The gastroduodenal effects of ghrelin and motilin may prove beneficial in the treatment of postoperative gastric ileus. In humans and other mammalian species, abdominal surgery and attendant manipulation of the viscera inhibit gastric emptying and digestive motor activity, which may result in postoperative ileus. Attempts to stimulate smooth muscle activity with prokinetics (eg, cisapride and acetylcholine) are often unsuccessful.¹¹⁴ In rats, ghrelin reverses postoperative gastric ileus.¹¹³

Effects on the Endocrine Pancreas

Ghrelin and GHS-R 1a mRNA are expressed in endocrine cells of the pancreas.^{37,48,121,122} Expression of

ghrelin has been reported in the pancreatic α -cells,¹²¹ although other investigators have reported that ghrelin is expressed in the pancreatic beta cells.⁶³ Ghrelin is not co-expressed with any known islet-derived hormone; thus, ghrelin-producing cells may be a newly recognized type of islet cell.¹²³

Published information regarding the effect of ghrelin on insulin secretion in humans and rats is conflicting,^{121,124,125} but most findings suggest that there is a negative association between ghrelin concentrations and insulin secretion.^{106,107,121,126,127} In humans, ghrelin induces a significant increase in plasma glucose concentrations and a decrease in insulin secretion.^{55,126} Coupled with the observation that treatment with GHSs, particularly the nonpeptidyl derivatives, induces hyperglycemia and insulin resistance in the elderly and in obese human patients, those findings suggest that ghrelin has an important role in the regulation of insulin secretion and glucose metabolism.^{128,129}

In healthy humans, hyperglycemia suppresses both baseline plasma concentrations of GH and GH release induced by GHRH.¹³⁰ The mechanism of the hyperglycemia-induced decrease in circulating GH is unclear. Acute hyperglycemia substantially decreases plasma ghrelin concentrations in healthy humans.¹³¹ Because ghrelin markedly stimulates GH secretion, the hyperglycemia-induced suppression of GH release may be caused, at least partly, by the decrease in plasma ghrelin concentrations.¹³¹

Cardiovascular Effects

Ghrelin receptors are widely distributed in cardiovascular tissues. In humans and rats, GHS-R 1a mRNA has been detected primarily in the heart, coronary arteries, and aorta.^{48,132} Ghrelin is synthesized and secreted by isolated human cardiomyocytes, in which it likely has paracrine or autocrine effects and may protect the cells from apoptosis.¹³³

Growth hormone improves cardiac performance in experimentally induced heart failure.^{134,135} In 1 study,⁸¹ prolonged treatment with GHSs protected aged rats against cardiovascular damage and improved cardiac performance after myocardial infarction, and enhanced left ventricular contractility in pigs with dilated cardiomyopathy. Long-term ghrelin administration improves cardiac contractility and cardiac output and reduces systemic vascular resistance in humans with chronic heart failure.¹³² Furthermore, it induces myocardial growth, improving the structure and function of the left ventricle.^{136,137} Interestingly, hexarelin, acylated ghrelin, and even unacylated ghrelin all prevent doxorubicin-induced death in cultured cardiomyocytes.¹³⁸ Because unacylated ghrelin does not activate the GHS-R 1a,⁵⁴ these data indicate that another subtype of GHS-R exists in cardiac tissue and that unacylated ghrelin has some biological activity.⁸¹ Thus, long-term administration of ghrelin may become a treatment strategy for patients with heart failure.¹³⁶

Antiproliferative Effects

Growth hormone secretagogue receptors are also found in human neoplastic tissues, such as mammary gland tumors and thyroid carcinoma cells.^{139,140} Ghrelin

and GHSs inhibit cell proliferation in thyroid tumor cells^{140,141} and breast cancer cells.¹³⁸ Nonacylated ghrelin also exerts antiproliferative actions.¹³⁹ Because unacylated ghrelin is unable to bind to the GHS-R 1a, these data suggest that the antiproliferative effects of acylated and unacylated ghrelin on cancer cells are mediated via a GHS-R subtype that is different from GHS-R 1a.¹⁴²

Conclusion

The isolation and characterization of ghrelin are landmarks in GH research and represent a major advancement in our understanding of GH regulation. Ghrelin is a gastric peptide that is active in the CNS, where it is involved in regulation of GH secretion and control of food intake. The widespread expression of GHS-Rs in central and peripheral tissues suggests that ghrelin may have many endocrine, paracrine, and possibly autocrine effects. Future challenges lie in improving our ability to diagnose and treat the different diseases associated with altered GH secretion. For example, the potential use of ghrelin in GH deficiency warrants investigation. In addition, ghrelin or ghrelin analogs may be useful in pathologic catabolic states such as wound and fracture healing, osteoporosis, severe burns, sepsis, excessive inflammation, multiple organ failure, and weakness in critically ill patients, all conditions in which the administration of moderate doses of GH has been effective.^{143,144} The orexigenic actions of ghrelin and its analogs may be harnessed to treat the pathologic forms of anorexia that accompany cancer and aging.¹⁴⁵ Whether ghrelin antagonists can be used to reduce food intake and be developed as a treatment for obesity remains to be investigated.

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