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JB Review

Structure, regulation and function of ghrelin

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Ghrelin is a stomach hormone that acts as an endogenous ligand of orphan G-protein-coupled receptor. Ghrelin is a 28-amino acid peptide existing in two major forms: *n*-octanoyl-modified ghrelin, which possesses an *n*-octanoyl modification on serine-3 and des-acyl ghrelin. Fatty acid modification of ghrelin is essential for ghrelin-induced growth hormone release from the pituitary and appetite stimulation. This acyl-modification of ghrelin is catalysed by ghrelin-*O*-acyl transferase recently identified. Despite the number of innovative advancements in this field of research, there are still many aspects of ghrelin function and biosynthesis process that remain to be clarified. Here, we review the current understanding of the structure, regulation and function of ghrelin; this review is intended for researchers who will be involved in this field in the future.

Keywords: acyl ghrelin/des-acyl ghrelin/GHSs/GHS-R/GOAT.

Abbreviations: ACTH, adrenocorticotropic hormone; AgRP, agouti-related protein; AMPK, 5′ AMP-activated protein kinase; ARC, arcuate nucleus; GH, growth hormone, GHRH, growth hormone releasing hormone; GHS, growth hormone secretagogue; GHS-R, growth hormone secretagogue receptor; GOAT, ghrelin-*O*-acyl transferase; GPCR, G-protein coupled receptor; IP_3, inositol 1,4,5-trisphosphate; MBOATs, the membrane-bound O-acyltransferases; MCFAs, medium-chain fatty acids; MCTs, medium-chain triacylglycerols; MTLRP, motilin-related peptide; NPY, neuropeptide Y; POMC, proopiomelanocortin; PRL, prolactin; 7TM, seven transmembrane domains.

History of Ghrelin Discovery

Kojima *et al.* (*1*) discovered ghrelin in 1999 as a 28-amino acid peptide from the rat stomach extracts. To understand why so many researchers were hunting for this hormone, and why the discovery took such a long time, we must go back to the identification of growth hormone secretagogues (GHSs).

It had been observed that some opioid peptide derivatives had weak growth hormone (GH)-releasing activity. In 1976, Bowers *et al.* (*2*) referred to these compounds as GHSs. Although the activity of early GHSs was very weak, many peptidyl derivatives with more potent GH-releasing activity were synthesized subsequently; including GHRP-6, first reported in 1984 (*3*). The non-peptide GHS L-692,429 was synthesized by Smith and colleagues (*4*) in 1993, suggesting the possibility of clinical use of GHSs because the non-peptide GHS is available for oral administration. Another non-peptide GHS, L-163,191 (MK-0677), was subjected to clinical trials, since it retained sufficient activity even when orally administered (*5*).

During this period, action of GHSs was gradually elucidated. Growth hormone releasing hormone (GHRH), the hormone that promotes GH secretion from GH-secreting cells in the anterior pituitary, acts on the GHRH receptor to increase intracellular cAMP, which serves as a second messenger (Fig. 1) (*6–10*). GHSs also act on a different receptor on GH-secreting cells in the anterior pituitary, increasing the intracellular Ca^{2+} concentration via an inositol 1,4,5-trisphosphate (IP_3) signal transduction pathway (Fig. 1). Growth hormone secretagogue receptor (GHS-R) was identified as a typical G-protein coupled receptor (GPCR) in 1996, and it was subsequently learned that GHSs stimulate phospholipase C, resulting in an increase in IP_3 and intracellular Ca^{2+} (*11*). GHS-R is expressed in the pituitary, hypothalamus and hippocampus; when it was discovered, this receptor was an orphan GPCR for which the natural ligand was not known (*11*, *12*, *13*). Therefore, a search for its endogenous ligand was actively undertaken using the orphan receptor strategy. Identification of the endogenous ligand was not easy, because it was mainly distributed in the stomach whereas GHS-R was mostly distributed in hypothalamus. Eventually, in 1999, ghrelin was identified as the endogenous ligand of GHS-R (*1*).

Structure of Ghrelin and of the Related Substances

Ghrelin

Ghrelin is a peptide consisting of 28 amino acids, and is unusual among peptide hormones of which Ser3 is *n*-octanoylated (Fig. 2a) (*1*). This modification, the first known case in mammals, is essential for ghrelin's activity (*1*).

The human ghrelin gene is localized on chromosome 3p25–26 (*14*). Both human and mouse ghrelin genes

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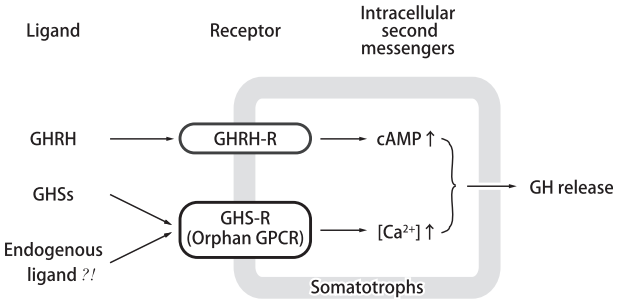

Fig. 1 A second messenger of GHRH and GHSs. GHRH acts on the GHRH receptor to increase intracellular cAMP, which serves as a second messenger. On the other hand, GHSs have also been shown to act on a GHS-R, increasing intracellular Ca^{2+} concentration via an IP_3 signal transduction pathway.

comprise five exons (*15*, *16*). There are two different transcriptional initiation sites in the ghrelin gene; one occurs at −80 and the other at −555 relative to the ATG initiation codon, resulting in two distinct mRNA transcripts (transcript-A and transcript-B) (*15*, *17*). The 28 amino acids of the functional ghrelin peptide are encoded in exons 1 and 2.

In rat and mouse stomach, a second type of ghrelin peptide has been purified and identified as des-Gln14-ghrelin (*18*). In ghrelin genes of these rodents, the codon for Gln14 (CAG) is used as an alternative splice acceptor site to generate two different ghrelin mRNAs. One mRNA encodes the ghrelin precursor, and another encodes a des-Gln14-ghrelin precursor. Except for the deletion of Gln14, des-Gln14-ghrelin is identical to ghrelin. This type of ghrelin also retains the *n*-octanoic acid modification, and has the same activities and potency as ghrelin. However, the level of des-Gln14-ghrelin in the stomach is low. Bovine and ovine ghrelins are 27-amino acid peptides which, like rat des-Gln14 ghrelin, lack the Gln14 residue. In the genes encoding these ghrelins, there is only one AG splice acceptor site between exons 2 and 3, resulting in the production of only one mRNA, which gives rise to the 27-residue ghrelin.

The non-acylated form of ghrelin, des-acyl ghrelin, is also present at significant levels in both stomach and blood (*19*). However, des-acyl ghrelin can neither bind GHS-R nor exhibit GH-releasing activity in rats. Nonetheless, food intake is induced by des-acyl ghrelin, administered by intracerebroventricular injection, to the same extent as ghrelin (*20*). Because the genome database does not contain another GPCR that resembles GHS-R, it is possible that des-acyl ghrelin acts by mechanisms independent of a GPCR. Further study will be required in order to determine the physiological significance of des-acyl ghrelin.

Ghrelin has been identified in many species. The amino acid sequences of human, rat and mouse ghrelin precursors are shown in Fig. 2b. The amino acid sequences of mature ghrelins are well conserved across mammals, including human, rat, mouse, rhesus monkey, mongolian gerbil, cow, pig, sheep and dog (*1*, *16*, *21*, *22*). Specifically, the 10 amino acids in the NH_2-termini are identical, strongly suggesting that this NH_2-terminal region is necessary for the activity of ghrelin. Mammalian ghrelin has a variety of functions—to stimulate GH release, food intake, fat accumulation, etc.

Among birds, chicken ghrelin is composed of 26 amino acids, and possesses 54% sequence identity with human ghrelin. Chicken ghrelin is predominantly expressed in the stomach, where it is present in the proventriculus (*23*). Administration of chicken ghrelin increased plasma GH levels in both rats and chicks, indicating that the stimulatory effect of ghrelin on GH secretion is evolutionarily conserved (*23*). On the other hand, intracerebroventricular injection of chicken ghrelin or of KP-102, a synthetic GHS, strongly suppressed feeding in neonatal chicks during the 2-h post-injection period, whereas ghrelin strongly stimulates feeding in mammals. Furthermore, the suppressive effect of feeding by chicken and rat ghrelin was almost identical in neonatal chicks. Thus, it is possible that the mechanisms for feeding of the neonatal chick are different from mammals.

Among amphibians, bullfrog ghrelin contains either 27 or 28 amino acids due to the differential processing of the COOH-terminal Asn residue (*24*). Bullfrog ghrelin possesses 29% sequence identity to human ghrelin. The unique amino acid sequence feature of bullfrog ghrelin is Thr3, corresponding to Ser3 in the mammalian ghrelins; bullfrog Thr3 is also modified, either by *n*-octanoic or *n*-decanoic acid. Bullfrog ghrelin mRNA is predominantly expressed in the stomach. Bullfrog ghrelin stimulates the secretion of both GH and PRL in dispersed bullfrog pituitary cells with potency 2–3 orders of magnitude greater than that of rat ghrelin. Bullfrog ghrelin, however, was only minimally effective in elevating plasma GH levels following intravenous injection into rats. Thus, although the ability of ghrelin to induce GH secretion is evolutionarily conserved, the structural differences between orthologous ghrelins result in species-specific receptor binding.

Fish ghrelins have been identified in rainbow trout, eel, tilapia and goldfish (*25–29*). Ghrelin has four isoforms in rainbow trout and two molecular forms in eel. In tilapia, ghrelin Ser3 is modified by *n*-decanoic acid, and the COOH-terminal end of the peptide possesses an amide structure. The goldfish ghrelin gene consists of four exons and three short introns. As in other vertebrates, fish ghrelins are also predominantly detected in the stomach. In organ-cultured tilapia pituitary, the release of GH and PRL are stimulated by eel ghrelin at a dose of 0.1 nM, and by tilapia ghrelin at a dose of 10 nM. Intracerebroventricular injection of *n*-octanoylated goldfish ghrelin (residues 1–19) stimulated food intake in goldfish.

GHS-R

The human ghrelin receptor gene has also been identified on chromosome 3, at position q26–27 (*14*). Ghrelin receptor is a typical GPCR, with seven transmembrane domains (7TM); it is expressed as two distinct mRNAs (*11*). The first, GHS-R type 1a, encodes a 7TM GPCR with binding and functional properties consistent with its role as the ghrelin receptor. The other GHS-R mRNA, type 1b, is produced by

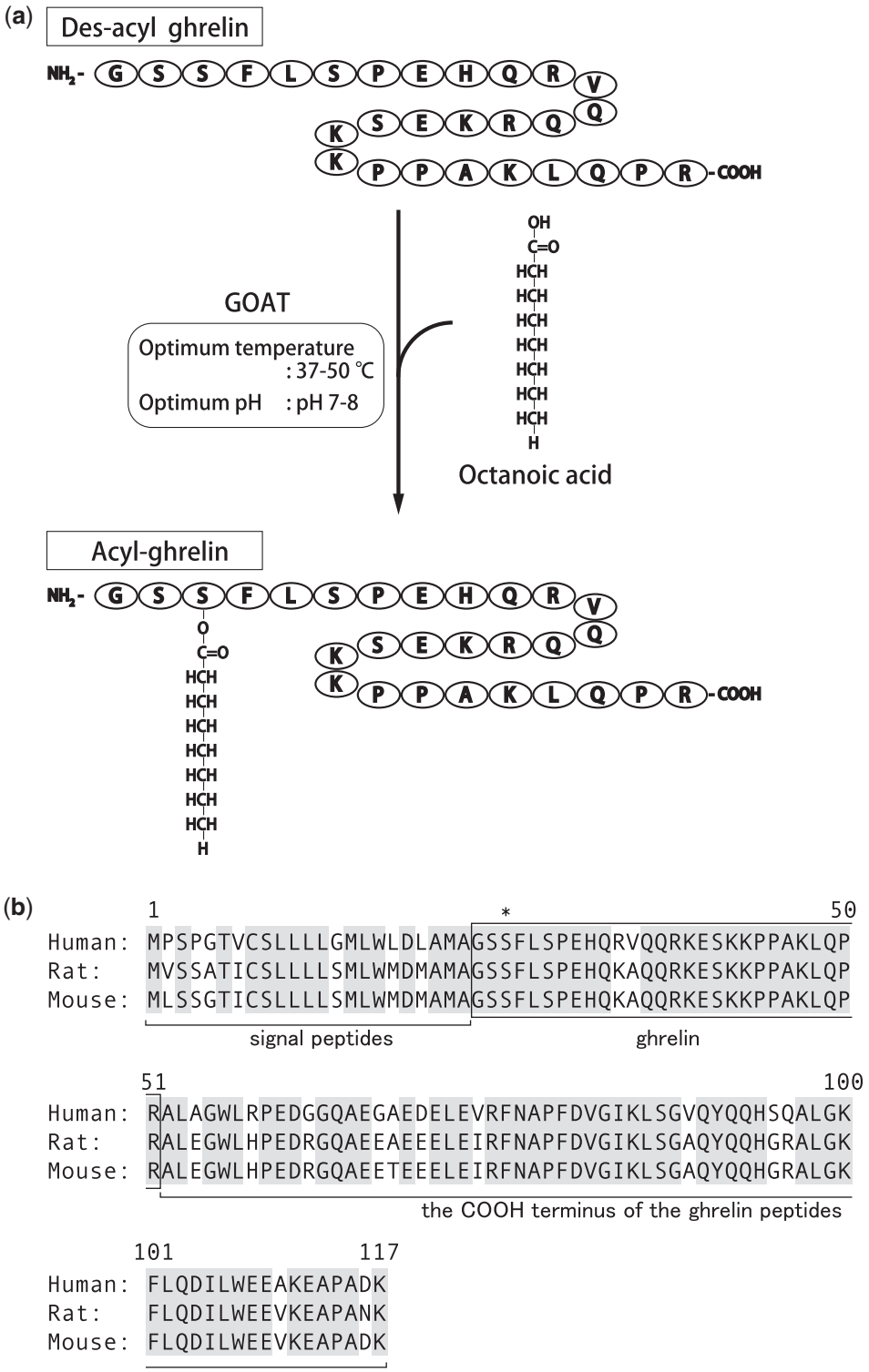

Fig. 2 (a) Structure of human ghrelin and the modification process of octanoic acid by GOAT. In rats, the 11th residue is lysine (K) and the 12th is alanine (a). (b) Amino acid sequences of ghrelin precursors in human, rat and mouse. Identical amino acids are coloured in grey. The asterisk shows the position of acyl-modified Ser3.

alternative splicing. The GHS-R gene consists of two exons; the first exon encodes TM1–TM5, and the second exon encodes TM6–TM7. Type 1b is derived from the first exon alone, and encodes only five of the seven predicted TM domains. The type 1b receptor is thus a COOH-terminal truncated form of the type 1a receptor, and is physiologically inactive.

Among GPCRs, ghrelin receptor is most similar to the motilin receptor (*30–32*). Alignment of the 28-amino acid peptide ghrelin and the 19-amino acid motilin reveals that they share eight amino acids. Although motilin can stimulate the GHS-R at a low level, ghrelin does not activate motilin receptor. After the discovery of ghrelin, the motilin-related peptide

(MTLRP) was identified; the amino acid sequence of MTLRP is identical to that of ghrelin-(1–18) (*33*). The ghrelin receptor is well conserved across all vertebrate species examined, including a number of mammals, bird and fish. This strict conservation suggests that ghrelin and its receptor serve essential physiological functions.

Ghrelin O-acyltransferase

An enzyme that catalyses the acyl-modification of ghrelin was discovered in 2008 by Yang *et al.* (*34*), using an innovative combination of bioinformatics and cell biology (Fig. 2). Using position-specific iterative BLAST and previously reported sequences of membrane-bound *O*-acyltransferases (MBOATs) from diverse species including prokaryotes, plants, humans and mice, they identified 16 MBOATs encoded by the mouse genome. They then isolated clones of all of these and tested them for their ability to catalyse octanoylation of ghrelin expressed in heterologous cell lines. Only one of these enzymes, MBOAT4, was found to be able to octanoylate ghrelin, and this enzyme was renamed ghrelin *O*-acyltransferase (GOAT). Distribution of this enzyme is limited to the gastrointestinal tract and testis, the peripheral tissues that express ghrelin. The optimum temperature of GOAT is 37–50°C, and its optimum pH range is pH 7–8 (*35*).

The origin of the modified medium-chain fatty acids (MCFAs) has not been determined. However, it is known that orally ingested MCFAs are directly utilized for acyl-modification of ghrelin (*36*). Ingestion of either MCFAs or medium-chain triacylglycerols (MCTs) specifically increases production of acyl-modified ghrelin without changing the total (acyl- and des-acyl-) ghrelin level. When mice ingest either MCFAs or MCTs, the acyl group attached to nascent ghrelin molecules corresponds to those of the ingested MCFAs or MCTs. Moreover, *n*-heptanoyl (C7:0) ghrelin, an unnatural form of ghrelin, can be produced in the stomach of mice following ingestion of *n*-heptanoic acid or glyceryl triheptanoate. Thus, it is clear that ingested fatty acids are directly utilized for acyl-modification of ghrelin (*17*).

Recently, Barnett *et al.* (*37*) described the design, synthesis and characterization of GO-CoA-Tat, a peptide-based bisubstrate analog that antagonizes GOAT. GO-CoA-Tat potently inhibits GOAT *in vitro*, in cultured cells and in mice. Intraperitoneal administration of GO-CoA-Tat in the concentration of 8 μmol/kg improves glucose tolerance in 2.5 g/kg of intraperitoneal glucose tolerance test. Moreover, the body weight gain in wild-type mice given MCT diet reduces by treatment with 11 μmol/kg GO-CoA-Tat for 1 month but not ghrelin-deficient mice; thus, its beneficial metabolic effects are due specifically to GOAT inhibition. GOAT is therefore, a useful target for future development of therapeutic compounds.

Obestatin

In 2005, Zhang *et al.* (*38*) used a bioinformatics approach to identify a 23-amino acid peptide derived from the ghrelin peptide precursor; this discovery brought exciting new insights to the gut peptide field. The authors named this peptide 'obestatin' because obestatin has the ability to inhibit food intake in mice by intraperitoneal or intracerebroventricular injection. In addition, the authors reported that peripheral injection of obestatin inhibited jejunal contraction, suppression of gastric emptying and decreased body-weight gain (*39–41*). However, their findings could not be reproduced by several groups, and must therefore be interpreted with caution.

Distribution and Regulation of Ghrelin

The acyl-modification of ghrelin is easily cleaved during sample extraction, and peptide samples are easily digested by a wide range of cellular proteases. Furthermore, in order to correctly measure the plasma concentration of ghrelin, it is necessary to use EDTA and aprotinin when collecting blood samples, and plasma must be collected into 1/10 volume of 1 N HCl (*19*, *42*). If the treated plasma samples are kept at −20 to −80°C, they are stable for at least 6–12 months. When measuring the tissue concentration of ghrelin, it is sufficient to inactivate proteases by boiling the tissues in water for 5–10 min (*43*, *44*). In human, the normal ghrelin concentration of plasma samples is 10–20 fmol/ml for *n*-octanoyl ghrelin and 100–150 fmol/ml for total ghrelin, including both acyl-modified and des-acyl ghrelins (*17*, *45*, *46*). In rats, ghrelin concentration in the stomach is 377.3 ± 55.8 fmol/mg for *n*-octanoyl ghrelin and 1779.8 ± 533.9 fmol/mg for total ghrelin (*17*, *19*). Thus, the concentration of *n*-octanoyl ghrelin is 10–20% that of des-acyl ghrelin.

Ghrelin is present in X/A-like cells, which account for ~20% of the endocrine cell population in adult oxyntic glands (*47*). Ghrelin-immunoreactive cells are also found in the duodenum, jejunum, ileum and colon. In the intestine, ghrelin concentration gradually decreases from the duodenum to the colon. Ghrelin is also secreted from other organs such as hypothalamus and pancreas of rats. In addition, ghrelin mRNA is expressed in various organs (*48*, *49*).

Several cell lines express ghrelin. TT cells, a human thyroid medullary carcinoma cell line, produced ghrelin mRNA; both conditioned medium and cellular extracts of TT cells contain ghrelin peptides (*50*). Cellular extracts of TT cells also contain both *n*-octanoyl ghrelin and des-acyl ghrelin. Other cultured cells that express ghrelin, include the kidney-derived cell line NRK-49F, gastric carcinoid ECC10 cells and the cardiomyocyte cell line HL-1 (*51–53*). Recently, Iwakura *et al.* (*54*) established a ghrelin-producing cell line MGN3-1 from a gastric ghrelin-producing cell tumour derived from transgenic mice in which SV40 Large T antigen was expressed under control of the ghrelin promoter. MGN3-1 cells produce a substantial amount of ghrelin at levels ~5000 times higher than in TT cells. In addition, MGN3-1 cells express two key enzymes: GOAT, for acyl modification and prohormone convertase 1/3 which is required for maturation of ghrelin. Moreover, MGN3-1 cells maintain physiological regulation of ghrelin secretion,

at least in regard to the suppression by somatostatin and insulin, which has been well established in *in vivo* studies. This cell line will be a useful tool for studying both production and secretion of ghrelin, as well as for screening of ghrelin production-modulating drugs.

The most known factor for the regulation of ghrelin secretion is feeding (*45*). Plasma ghrelin concentration increases when fasting, and decreases after food intake. The factors involved in the regulation of ghrelin secretion have not yet been identified. Blood glucose level may be a most probable candidate: oral or intravenous administration of glucose decreases plasma ghrelin concentration (*55*). Because gastric distension by water intake does not change ghrelin concentration, mechanical distension of the stomach alone clearly does not induce ghrelin release (*56*, *57*). Plasma ghrelin concentration exhibits a nocturnal increase. Plasma ghrelin concentration is low in obese people and high in lean people (*55*, *58–62*, *63*). Exogenous GH decreases stomach ghrelin mRNA expression and plasma ghrelin concentration, but does not affect stomach ghrelin stores (*64*).

There may be a relationship between sequence variation in the ghrelin gene and obesity (*65–67*). In humans, two polymorphisms have been reported: Arg51Gln and Leu72Met. For both polymorphisms, allelic frequencies are similar between obese patients and controls. However, obese patients with the Met72 allele became obese earlier than patients homozygous for the wild-type Leu72 allele, suggesting that the polymorphism may affect ghrelin's activity. The Arg51Gln mutation changes the sequence of the COOH-terminal processing site of the ghrelin peptide, within its precursor protein, from Pro-Arg to Pro-Gln; this mutation prevents the normal cleavage necessary to produce mature ghrelin.

Physiological Functions of Ghrelin

GH-releasing activity by ghrelin

Ghrelin is a hormone that has a lot of physiological functions (Table 1). One of its primary functions involves its strong GH-releasing activity (*1*, *68–72*). The maximal stimulation effected by ghrelin is two to three times greater than that of GHRH, in both rats and human. GH release reaches its peak ~5–15 min after intravenous ghrelin injection. A single intracerebroventricular administration of ghrelin also increases rat plasma GH concentration (*70*). There are several models regarding the mechanism of ghrelin's stimulatory effect on GH secretion. Ghrelin stimulates GH release from primary pituitary cells, indicating that ghrelin can act directly on the pituitary (*1*). On the other hand, the involvement of the hypothalamus in ghrelin-mediated stimulation of GH release has also been suggested. Furthermore, the induction of GH release after ghrelin injection is dramatically decreased when the vagus nerve is cut, indicating that the vagus nerve is required for the maximal stimulatory effects of ghrelin (*73*, *74*). A synergistic effect of ghrelin and GHRH is also important. Co-administration of ghrelin and GHRH results in more GH release than does either GHRH or ghrelin alone (*69*, *75*). This finding implies that GHRH is necessary for GH release to be maximally effective in inducing GH release.

Appetite regulation by ghrelin

Ghrelin is only a hunger signal from peripheral tissues. Intravenous and subcutaneous injections of ghrelin increase food intake; likewise, peripherally injected ghrelin stimulates hypothalamic neurons and food intake (*76–81*). Because the rate at which peripheral ghrelin passes the blood–brain barrier has shown to be very low, peripheral ghrelin must activate the appropriate hypothalamic regions via an indirect pathway.

Table I. Physiological functions of ghrelin in human or rats.

Functions	Effects	Organs	Species	References
Pituitary hormone secretions				
GH	↑	pituitary	humans, rats	(*1*, *68–72*)
PRL	↑ (weak)	pituitary	humans	(*72*)
ACTH	↑ (weak)	pituitary	humans	(*72*)
Appetite regulations				
Food intake	↑		humans, rats	(*76*, *78*, *80*, *81*)
AMPK activity	↑	hypothalamus	rats	(*98*)
Lipid metabolisms				
Adiposity	↑		rats	(*99*)
Triglyceride	↑	white adipose tissue, liver	rats	(*100*)
Glucose metabolisms				
Blood glucose	↑		humans	(*96*)
Insulin	↓	Pancreas	humans	(*96*)
Cardiovascular functions				
Blood pressure	↓		humans, rats	(*89*, *90*)
Cardiac output	↑		rats	(*101*)
Gastric functions				
Gastric acid secretion	↑	Stomach	rats	(*102*)
Gastric movement	↑	Stomach	rats	(*88*)
Bone metabolism				
Osteoblast differenciation	↑	Bone	rats	(*103*)
Bone mineral density	↑	Bone	rats	(*103*)

↑, stimulate; ↓, decrease.

The localization of ghrelin receptors on vagal afferent neurons in the rat nodose ganglion suggests that ghrelin signals from the stomach are transmitted to the brain via the vagus nerve (*73*, *82*). As noted above, vagotomy actually inhibits the ability of ghrelin to stimulate food intake (*73*). A similar effect is also observed when capsaicin, a specific afferent neurotoxin, is applied to vagus nerve terminals to induce sensory denervation. Moreover, fasting-induced elevation of plasma ghrelin is completely abolished by sub-diaphragmatic vagotomy or atropine treatment (*74*). In summary, ghrelin is secreted primarily from stomach in response to hunger and starvation, circulates in the blood and serves as a peripheral signal, informing the central nervous system (via vagus nerve) to stimulate feeding.

Ghrelin is also identified in hypothalamus. Ghrelin-containing neurons are found in the arcuate nucleus (ARC) of the hypothalamus, a region involved in appetite regulation (*1*). In fact, intracerebroventricular injection of ghrelin increases cumulative food intake and decreases energy expenditure, resulting in body weight gain (*77*, *79*, *83–85*). This orexigenic effect of hypothalamic ghrelin is regulated through a neuronal network involving food intake. To stimulate the release of the orexigenic peptides, ghrelin-containing neurons send efferent fibers onto neuropeptide Y (NPY)- and agouti-related protein (AgRP)-expressing neurons. On the other hand, to suppress the release of the anorexigenic peptide, ghrelin-containing neurons send efferent fibers onto pro-opiomelanocortin (POMC) neurons (*86*). The ARC is also a target of leptin, an appetite-suppressing hormone produced in adipose tissues (*87*). Leptin directly inhibits appetite-stimulating effects of NPY and AgRP, whereas hypothalamic ghrelin augments NPY gene expression and blocked leptin-induced feeding reduction. Thus, ghrelin and leptin have a competitive interaction in feeding regulation.

Other functions of ghrelin

Intravenous administration of ghrelin increases gastric acid secretion and stimulates gastric motility in a dose-dependent manner (*88*). The maximum response to ghrelin, in terms of gastric acid secretion, is almost as high as that elicited by subcutaneous treatment with histamine (3 mg/kg). These responses to ghrelin were abolished by pre-treatment with either atropine or bilateral cervical vagotomy, but not by a histamine H2-receptor antagonist.

An intravenous bolus of human ghrelin decreased mean arterial pressure without changing the heart rate (*89*, *90*). The decrease in mean arterial pressure induced by ghrelin seems not to occur through direct action on the circulatory system, but by its action on the nucleus of the solitary tract (*91*, *92*). Microinjection of ghrelin into this nucleus significantly decreased the mean arterial pressure and heart rate. This injection also suppressed sympathetic activity.

There are many reports on the regulation of insulin secretion by ghrelin (*48*, *93–95*). Date *et al.* (*48*) reported that ghrelin stimulates insulin release in the presence of high levels of glucose (8.3 mM) that could independently cause insulin release from cultured islet cells. In contrast, ghrelin had no effect on insulin release in the context of a basal level of glucose (2.8 mM). On the other hand, ghrelin reduces insulin secretion and induces hyperglycaemia in humans (*96*). Thus, the regulation of insulin secretion by ghrelin is closely related to the blood glucose level. Ghrelin originating from pancreatic islets may be a major regulator of insulin secretion. Antagonism of the pancreatic ghrelin can enhance insulin release to meet increased demand for insulin in high-fat diet-induced obesity of mice (*97*). Since there is a difference of a result among researchers about the role of the ghrelin on insulin secretion, further research is expected.

After the discovery of ghrelin, it was realized that the stomach is an important organ not only for digestive function, but also for the regulation of energy metabolism and the secretion of GH. In addition, the novel octanoylated structure of ghrelin represented a new finding in biochemistry. The newly identified enzyme that catalyses the acyl-modification of ghrelin, GOAT, strongly provides the secretory machinery of the ghrelin and may herald new progress in our understanding of fatty acid metabolism. The mechanism of ghrelin synthesis still remains unclear, but will hopefully be elucidated by future research.

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Conflict of interest

None declared.

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