MINIREVIEW

Ghrelin Expression and Actions: A Novel Peptide for an Old Cell Type of the Diffuse Endocrine System

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Ghrelin is a gastric peptide involved in food intake control and growth hormone release. Its cell localization has been defined in distinct ghrelin cells of the gastric mucosa in humans and other mammals. Ghrelin production was also described in a number of other sites of the diffuse endocrine system, including the pituitary, thyroid, lung, pancreas, adrenal gland, and intestine. In addition, ghrelin cells were identified early during fetal life and in the placenta and gonads. Finally, endocrine growths and tumors of the diffuse endocrine system may present ghrelin-producing cells, and in a few cases high levels of circulating ghrelin were reported. Besides its well-defined orexigenic role, ghrelin is likely to exert a local paracrine role similar to other brain-gut axis hormones. This review aims to summarize recent data on ghrelin cell distribution in the diffuse endocrine system and discuss local and general ghrelin function during development, adulthood, and endocrine tumor development. Exp Biol Med 229:1007–1016, 2004.

Key words: ghrelin; growth hormone secretagogue; diffuse endocrine system; stomach; electron microscopy; P/D_1

The Structure of Ghrelin

Ghrelin, a novel, motilin-related, growth hormone (GH)–releasing, and orexigenic peptide, was originally isolated from the stomach (1, 2). The ghrelin peptide is made up of 28 amino acid residues (molecular weight, 3314), displays a high degree of homology in various mammals (Fig. 1), and derives from a 117–amino acid propeptide named preproghrelin (1). Ghrelin is the first natural hormone to be identified in which the serine residue in position 3 (Ser^3) was esterified with n-octanoic acid, a peculiar posttransductional modification capable of increasing the lipophilicity of the molecule. The strong GH-releasing activity of ghrelin is mediated by the activation of the growth hormone secretagogue (GHS) receptor type 1a (GHS-R1a) (3, 4). Interestingly, ghrelin mostly circulates as des-octanoyl ghrelin (i.e., without the esterification of Ser^3), a form of the protein that is void of endocrine properties and unable to stimulate the GHS-R1a (1, 5–7).

Acylated ghrelin crosses the blood-brain barrier in both directions using a saturable transport system that requires the presence of the unique octanoyl residue of the ghrelin molecule. In contrast, desacyl ghrelin crosses the blood-brain barrier by nonsaturable passive mechanisms and is retained by the brain once within the central nervous system (8).

After the discovery of ghrelin, another form of the protein was isolated and named des-Gln^{14}-ghrelin. This is a 27–amino acid protein with a peptidic sequence similar to that of ghrelin but lacking the Gln in position 14. Similar to ghrelin, this molecule too requires the n-octanoylation of Ser^3 for its biological activity. These two peptides, so similar in chemical structure and pharmacologic activity, result from a single gene that produces two alternative, distinct messenger RNAs (mRNAs) (9). By using a cell line stably transfected with the human GHS-R1a, it was shown that synthetic peptides that encompass the first four or five residues of ghrelin and carry the esterification of Ser^3 were

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Human	GSSFLSPEHQRVQQRKESKKPPAKLQPR
Rat	GSSFLSPEHQKAQQRKESKKPPAKLQPR
Mouse	GSSFLSPEHQKAQQRKESKKPPAKLQPR
Pig	GSSFLSPEHQKVQQRKESKKPAAKLKPR
Dog	GSSFLSPEHQKLQQRKESKKPPAKLQPR
Sheep	GSSFLSPEHQKL-QRKEPKKPSGRLKPR
Cattle	GSSFLSPEHQKL-QRKEAKKPSGRLKPR

Figure 1. Amino acid sequence of ghrelin in mammals. Amino acid residues that differ from the human sequence are underlined.

capable of activating the human GHS-R1a as efficiently as the full-length ghrelin (5, 10). Based on these *in vitro* results, it was postulated that the active core required for the activation of the receptor was the tetrapeptide Gly-Ser-Ser(n-octanoyl)-Phe. However, similar short ghrelin analogs did not stimulate GH release *in vivo* in the rat (11), suggesting that the C-terminal portion of the molecule could play a key role in determining the bioactive conformation of ghrelin.

The Diffuse Endocrine System (DES)

The DES embraces a number of specialized endocrine cells located within almost all organs of the major apparatuses, including the respiratory system, digestive system, and urinary system. The pituitary, thyroid, parathyroid, and adrenal glands also traditionally make up the DES. All DES cells display similar machinery for the storage and release of specific hormones. In particular, the well-known electron-dense granule of the endocrine cell, defined as a large, dense core vesicle, is the source of several markers of endocrine differentiation, including chromogranin A with related fragments and the vesicular monoamine transporter isoforms 1 and/or 2 (VMAT1 and VMAT2) (12, 13). The large, dense core vesicle may display different ultrastructural features for size, shape, and electron density, allowing a cell-specific classification.

The DES of the gastroenteropancreatic tract is probably the largest endocrine organ of the whole human body (14). Gut DES cells release hormones into the bloodstream to act on distant tissues and/or to participate in the local control of secretion, absorption, motility, mucosal cell proliferation, and, possibly, immune barrier. Such functions are exerted by at least 13 different epithelial, endocrine cell types of endodermal origin, initially classified on the basis of their granule ultrastructures and named with letters (15). The subsequent hormone isolation and the use of immunological *in situ* methods assigned at least one specific hormone for each granule and cell type, allowing a relatively complete morphofunctional classification (Table 1; Ref. 16). However, far from being a frozen catalogue, the endocrine cell classification is susceptible to changes and renovation on the discovery of novel hormones and/or reflecting new findings from endocrine cell biology (17).

The Ghrelin Cell

Light and Electron Microscopy of the Gastric Ghrelin Cell. The original description of gastric ghrelin cells was performed in rodents (1, 2, 18). The ghrelin cell was identified as a fairly distinct round cell of the midportion of the oxyntic gland at ultrastructure displaying X/A-like granules. One of the two original reports was

Table 1. The Endocrine Cells of the Human Gastrointestinal Tract[a]

		Stomach		Small intestine			Large intestine		
Cell	Main product	CF	A	D	J	I	Ap	C	R
P/D_1	Ghrelin	+	r	r	r	r			
EC	Serotonin[b]	+	+	+	+	+	+	+	+
D	Somatostatin	+	+	+	+	r	r	R	r
L	GLI/pYY			r	+	+	+	+	+
A	Glucagon	f							
PP	PP			f					
ECL	Histamine	+							
G	Gastrin		+	+					
CCK	CCK			+	+	r			
S	Secretin			+	+				
GIP	GIP			+	+		r		
M	Motilin			+	+		r		
N	Neurotensin			r	+		+		

[a] Modified from Solcia et al (16). CF, corpus fundus; A_t, antrum; D, duodenum; J, jejunum; I, ileum; Ap, appendix; C, colon; R, rectum; +, presence of cells; r, presence of rare cells; EC, enterochromaffin; GLI, preproglucagon fragments; pYY, peptide tyrosine tyrosine; f, presence of cells in fetus and newborn; PP, pancreatic polypeptide; ECL, enterochromaffin-like; CCK, cholecystokinin; GIP, gastric inhibitory polypeptide.
[b] Additional products such as substance P, neurokinins, opioids, guanylin, and other peptides.

performed on mouse stomach and indicated that, besides chromogranin A, a subpopulation of ghrelin cells also co-expressed serotonin and somatostatin, probably a species-specific feature (2). Overall, the reported evidence indicated the endocrine nature of the ghrelin cell and supported its inclusion in the DES of the stomach of rodents.

Similarly, in humans, ghrelin cells were found to correspond to a fraction of cells positive for chromogranin A and VMAT2, although they were negative for histidine decarboxylase, serotonin, and somatostatin (18, 19). These findings indicate that in humans as in rodents the ghrelin cell is distinct from the other three better-known cell types of the oxyntic mucosa, namely, the histamine-producing enterochromaffin-like (ECL) cell, the somatostatin-producing D cell, and the serotonin-producing enterochromaffin (EC) cell. Of note, both the D and ECL cells are well represented in the oxyntic mucosa and deeply involved in the local control of gastric acid output (20). At ultrastructural analysis, human ghrelin cells are characterized by round, compact-to-thin, haloed secretory granules of a mean diameter of approximately 140 nm, with features consistent with the P/D_1 cells of previous studies (21–23). Single immunogold labeling with ghrelin antiserum exclusively labeled P/D_1 granules, confirming the P/D_1 cells as ghrelin cells (19). Double immunogold labeling with ghrelin and VMAT2 sera demonstrated that ghrelin cells co-express VMAT2 in their granules, in contrast with ECL cells, which displayed only VMAT2 labeling (19). Of note, ghrelin cells display different granule size and morphologic features in different species (19). In dog, the ghrelin cell exhibits large granules of approximately 270 nm (Fig. 2A), thus corresponding to the previously characterized X cells (24), which in rat are approximately 180 nm, as A-like or X cells (25, 26), and in humans are approximately 140 nm (Fig. 2B), as P/D_1 (19).

Overall, the reported evidence confirms that in humans, too, the gastric ghrelin cell is an epithelial endocrine element of the DES of the stomach. Accounting for approximately 20%–30% of the oxyntic endocrine population, ghrelin cells are the second most frequent endocrine cell type after the ECL cell, pointing to a relevant role of ghrelin in the physiology of the stomach.

The Ghrelin Cell in the DES. Ghrelin immunoreactivity was described in distinct cells of the gastrointestinal tract, pancreas, pituitary, lung, and thyroid. In the gastrointestinal tract of rodents and humans, ghrelin cells were described with decreasing frequency in the antrum and upper intestine, whereas no (human) or rare (rat) ghrelin cells were observed in the large intestine (2, 18, 19, 27, 28). Interestingly, although in the oxyntic mucosa ghrelin cells consistently show no connection with the lumen (so-called closed-type endocrine cell), in other parts of the gut they also display a bottle shape, with evident connection toward the lumen (so-called open type) (28). This finding indicates that luminal regulatory stimuli may act on open-type ghrelin cells and suggest a potentially distinct physiological role.

Controversial results were reported in the pancreas. In humans, ghrelin expression was variably observed in insulin B cells (29) or glucagon A cells as in rats (30). On our side, we were unable to detect significant ghrelin cells in adult human islets, although ghrelin cells were frequently observed during fetal life (19). Interestingly, some authors have proposed that in the rat fetus, in contrast to the adult, the pancreas and not the stomach is a major source of immunoreactive ghrelin (31). Others confirmed our developmental data in humans and identified ghrelin immunoreactivity and mRNA in rare cells void of any known insular hormone but developmentally related to A cells observed in adult samples of both humans and rat (32, 33). Independent from the cell type, ghrelin expression in adult pancreatic islets is restricted to a minority of cells if any, suggesting a relatively modest role for ghrelin in islet physiology.

Of other known DES sites, in humans, during adult life rare ghrelin cells were described in the lung (19, 34) but not in the thyroid (35). In the pituitary, ghrelin-expressing cells were observed in distinct subpopulations in humans (36, 37) and in rat were found to correspond to somatotrophs, lactotrophs, and thyrotrophs (38).

Overall, in humans, the ghrelin cell of the respiratory system and the gastrointestinal tract reasonably corresponds to the P/D_1 type that previous ultrastructural studies identified in such tissues. In the pituitary and thyroid, it is likely that ghrelin expression can be induced on specific physiological stimuli and the hormone co-stored with others, as observed in many other endocrine cell types. In light of such evidence, the mass ghrelin production from the stomach appears to reflect its most important systemic physiological role. Conversely, the limited production of ghrelin in other sites by distinct, though rare, cells suggests a local paracrine control of the specific function(s) of various organs.

Other Sites of Ghrelin Expression. The presence of ghrelin-positive cells in the nucleus arcuatus of the hypothalamus (39, 40) and in a distinct group of neurons near the third ventricle projecting onto the hypothalamic circuitry is possibly involved in energy homeostasis (41, 42). However, the location of the few ghrelin-positive neurons identified depends on the epitope recognized by the antiserum used in immunohistochemical analysis. Several authors have questioned whether ghrelin expression really takes place in the central nervous system, and recent data obtained by real-time polymerase chain reaction show undetectable levels in the cerebral cortex or hypothalamus of the rhesus monkey (43). For this reason, it cannot be ruled out that ghrelin found in the hypothalamus may possibly derive from the periphery.

Of various other tissues, ghrelin expression was observed in the gonads of both rat and humans (44–47), human placenta (48), and the immune system of humans,

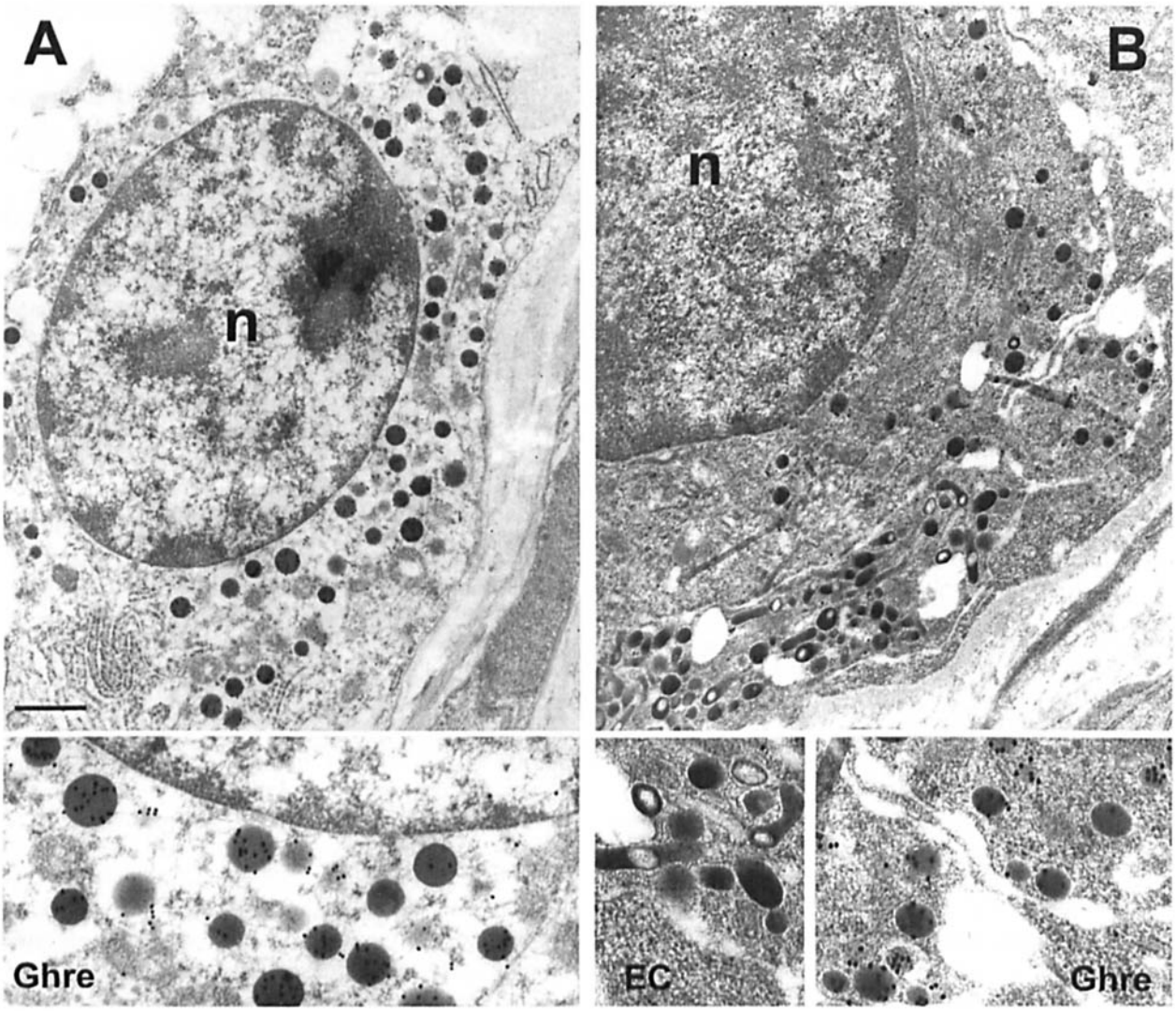

Figure 2. Ultrastructure of the ghrelin cell. (A) Dog ghrelin cell showing the typical round shape with several large, round, solid, electron-dense granules of X type heavily labeled for ghrelin antibody (19), as depicted in the lower part at higher magnification (Ghre, detail of A). (B) Human ghrelin cell with abundant, small, round, electron-dense granules, juxtaposed to a cytoplasmic extension of a serotonin-producing enterochromaffin cell (lower left middle part of the micrograph) with variably shaped granules; note that the irregular, pear-shaped enterochromaffin cell (EC) granules are void of gold particles, opposite to the rich labeling observed in P/D_1 granules of the ghrelin cell, as depicted in the lower part at higher magnification (Ghre, detail of B). Scale bar: A, 700 nm, and Ghre, 350 nm; B, 560 nm, and EC and Ghre, 280 nm. LWR, aldehyde/London white resin; immunogold, 20 nm; uranyl acetate and lead citrate counterstain; n, nucleus.

although at mRNA level only (49). In addition, ghrelin mRNA was amplified from multiple tissues, but for many of these any cellular confirmatory assessment is still lacking (50). Interestingly, production of ghrelin in the mouse kidney was shown in greater abundance than in mouse plasma (51).

Ghrelin Cells and Development

Ghrelin is expressed in many tissues during early development. Ghrelin cells were detected in the first trimester as early as 8–10 weeks of gestation in the thyroid, lung, gastrointestinal tract, and pancreas in humans (19, 32, 34, 35) and at corresponding gestational ages in rat tissues inclusive of the pituitary gland (33). These data together with the expression of ghrelin in the placenta (48) support an important role for ghrelin during early life.

Ghrelin Cells and Tumors

Ghrelin immunoreactive cells were observed in well-differentiated endocrine tumors of the pituitary gland, lung, stomach, intestine, and pancreas (27, 29, 35–37, 52–57). Ghrelin cells were most frequently seen in pituitary and gastric endocrine tumors, as expected. In addition, ghrelin expression was reported in testicular tumors (45) and, only at mRNA level, in prostatic cancer (58). Notably, high levels of circulating ghrelin were reported so far in two

patients had well-differentiated pancreatic (59) and gastric endocrine tumors, respectively.[2]

The Multifacet Physiology of Ghrelin

Ghrelin and the Hypothalamic and Pituitary Function. Similar to the synthetic GHSs, ghrelin dose-dependently stimulates GH release from primary pituitary cells in a dose-dependent manner (1). However, its activity is much more evident *in vivo* both in experimental animals and in humans (60–63).

Intravenous ghrelin administration effectively stimulates the secretion of GH; a single intravenous bolus of the peptide elicits a rapid onset of plasma GH, which reaches the peak within 5–15 mins in the rat and within 15–20 mins in humans (1).

It is remarkable that the GH-releasing activity of ghrelin and the GHSs are much more consistent than those of maximal doses of growth hormone–releasing hormone (GHRH) in humans (64). However, experiments performed in rats indicate that the GH-releasing activity of the hormone also is related to the route of administration, because it is more pronounced by the peripheral route (iv) than by the central one (65). Although the predominant effect is the secretion of GH, the activity of these molecules is not fully specific for GH release. They can in fact elicit a small but consistent increment of the plasma concentrations of prolactin, ACTH, and cortisol (1, 64, 66).

Previous studies demonstrated that the GH-releasing action of GHSs was partially reduced by GHRH deficiency, indicating that this deficiency was essential for their full pharmacological activity (66). Similarly, the endocrine activity of ghrelin *in vivo* depends not only on the route of administration but also on the functional integrity of the GHRH system. In fact, in the adult rat, pretreatment with an antibody against GHRH, a functional antagonist of GHRH (67), or the lesion of the arcuate nucleus is able to reduce ghrelin and GHS efficacy (65).

At variance with the adult rat, we have reported that in 10-day-old rats the complete lack of GHRH and somatostatin, obtained by passive immunization against both factors, did not change the GH-releasing activity of GH-releasing peptide 6 or hexarelin, indicating that GHRH activation may represent an intermediate, although not obligatory, step of GHS action (68).

It is noteworthy that, *in vivo*, co-administration of ghrelin and GHRH produces a synergistic effect on the release of GH but not on the release of prolactin, ACTH, and cortisol (69). Conversely, the secretory response to ghrelin is not amplified by the combined administration of hexarelin, a synthetic GHS (64). The synergistic effect of ghrelin and GHRH probably derives from an interaction that takes place in the hypothalamus, because it is not present *in vitro* in cultured pituitary cells (70). Among the possible explanations of this phenomenon, we can consider both that the GHS can act as functional antagonists of somatostatin (71) and that ghrelin and the GHS might promote the release of an unknown hypothalamic factor, the "U" factor, that would be responsible of the aforementioned mechanism (72).

Even if ghrelin is the most potent GHS so far discovered, being on a molar basis even more potent than hexarelin and GH-releasing peptide 2 (64, 67), its plasma level appears not to be regulated by GH in a classic feedback mechanism. In fact, in adult patients with isolated GH deficiency, ghrelin plasma levels are similar to those of control subjects and do not decrease after 1 year of GH replacement therapy (73). On the other hand, it has been recently shown that, in humans, the iv administration of somatostatin or cortistatin-14, a natural analog of somatostatin receptors, strongly inhibits the spontaneous release of ghrelin, indicating the existence of a tight functional relationship between the two systems. Although the mechanism responsible for such an inhibitory effect has not been so far defined, it is possible that the actions of somatostatin and cortistatin-14 are mediated by interactions with the known somatostatinergic receptors, largely expressed in the gastric mucosa (74).

It was not surprising that ghrelin, a gastrointestinal hormone, is endowed with endocrine effects on the pancreatic hormones. However, discordant data were reported in rat, because ghrelin was shown to stimulate insulin secretion both *in vitro* and *in vivo* (30, 75, 76), but in the perfused rat pancreas ghrelin proved to antagonize the glucose-stimulated insulin release (77). In keeping with the latter finding, different reports suggest that ghrelin may inhibit, at least transiently, insulin secretion in humans (78, 79). Our understanding of the effects of ghrelin on insulin secretion is even more complicated by the demonstration that, in humans, short-term ghrelin administration produces an increment of glucose blood levels followed by a reduction of insulin levels (80), a result consistent with the already reported effects in elderly (81) and obese patients (82) after long-term treatment with synthetic GHSs.

Ghrelin, Food Intake, and Body Weight. Before the discovery of ghrelin, some studies demonstrated that the GHSs administered peripherally or centrally are orexigenic in the rat (83–85). This effect appears not to be strictly related to their GH-releasing properties and is probably mediated by different receptors (84). The orexigenic effect is also independent from GHRH but requires the integrity of the hypothalamic nuclei and the involvement of neuropeptide Y (NPY), a potent stimulator of the appetite of hypothalamic origin (85). Similar to synthetic GHSs, ghrelin too promotes feeding, with an efficacy similar to that of NPY (86–88). This is further supported by the observation that the central administration of an antighrelin antiserum

[2] K. Öberg, personal communication. While this article was in the proof stage, the gastric tumor case was published. (Tsolakis AV, Portela-Gomez GM, Stridsberg M, Grimelius L, Sundin A, Eriksson BK, Öberg KE, Janson ET. Malignant gastric ghrelinoma with hyperghrelinemia. J Clin Endocrinol Metab 89:3739–3744, 2004)

twice daily for 5 days decreased significantly both daily food intake and body weight (89).

The mechanism of action of ghrelin is not completely defined; however, much experimental evidence would recognize the involvement of NPY and the agouti-related protein (AGRP), another orexigenic peptide of hypothalamic origin. In rat, both short-term and long-term treatment with ghrelin caused an increase of the hypothalamic mRNA levels of NPY and AGRP (90). In addition, ghrelin effects could be antagonized by co-administration with antagonists of AGRP or antagonists of the Y1 or Y5 receptor for NPY (91), as well as by the destruction of the arcuate nucleus (65). Finally, the persistence of the orexigenic effect of ghrelin in NPY knockout mice would indicate that the AGRP system can substitute for the lack of NPY (86).

The increase of appetite is associated with body weight increase. However, the latter does not depend on increased somatic or muscular development, which are typical effects of GH, but instead derives from increased adipogenesis and reduced lipid metabolism (92).

Ghrelin and the Gastric Function. It is not surprising, based on its gastrointestinal origin, that ghrelin can influence stomach activity, in particular motility and acid secretion. In urethane-anesthetized rats, central administration of the peptide evokes an increase of gastric motility and acid secretion (93, 94). However, in conscious rats ghrelin effectively inhibits gastric acid secretion after central and systemic administration, suggesting a possible physiological role of ghrelin in the control of gastric secretory function (95). The central long-lasting gastric inhibitory action of ghrelin seems appropriate from a teleological point of view, considering that fasting increases ghrelin serum levels and that during fasting a decrease in acid secretion is relevant for the maintenance of gastric mucosal integrity. It has also been shown that the peripheral or central administration of ghrelin exerts a potent and dose-related protective action against ethanol-induced gastric ulcers, an effect mediated by endogenous nitric oxide release and that requires the integrity of sensory nerve fibers (96).

Other Functions of Ghrelin. We have reported for the first time, to our knowledge, that a prolonged treatment with hexarelin could protect the hearts of rats with experimental GH deficiency from the ischemia-reperfusion damage through a mechanism independent from GH secretion, because the effect was also present and even magnified in hypophysectomized rats (97). However, not all of the GHSs share the same efficacy in preventing the ischemia-reperfusion damage, again indicating the possible involvement of different receptors in their mechanism of action (97). This hypothesis is further supported by our recent demonstration that ghrelin is much less effective than hexarelin in protecting myocardium from the ischemia-reperfusion damage in hypophysectomized rats (98). The different pharmacological activity could depend on activation of different receptor species. In the heart, hexarelin binds primarily to CD36, a type B scavenger receptor, whereas ghrelin and the other less effective GHSs would activate mainly the GHS-R1a (99).

The cardiac activity of ghrelin is different, however, in different animal species. In humans, in fact, at variance to rats, the short-term administration of the peptide was found effective in reducing the afterload and in increasing cardiac output both in healthy patients and in patients with severe GH deficiency without any change in heart rate (100).

Recent studies revealed that ghrelin and some synthetic GHSs also possess an antiproliferative activity on different tumor cell lines (58, 101). The expression of GHS receptor subtypes has been found also in tumor tissues from organs that do not express these receptors in physiological conditions, such as the breast (102). It has also been reported that des-acyl ghrelin, reportedly a biologically inactive peptide unable to bind the GHS-R1a and to stimulate GH release both *in vivo* and *in vitro*, caused inhibition of tumor cell proliferation, indicating that it may activate a receptor distinct from the GHS-R1a (102).

Because the secretion of ghrelin is regulated by energy balance, it is likely that the plasma levels of ghrelin are lower in obese patients (103) and higher in anorexia nervosa patients (104) compared with healthy subjects. Generally, in humans, circulating ghrelin is inversely related to body mass index, adipose tissue mass, dimension of the adipocytes, and insulin and leptin plasma levels (103, 105). It is then possible that higher or lower secretion of ghrelin would compensate for metabolic dysregulations such as those observed in such pathologic situations. Possible mutations of the ghrelin gene have also been proposed to explain the impaired regulation of body weight in obese mammals, as suggested by a study that reported an association between mutations in the preproghrelin/ghrelin gene and obesity (106).

Finally, ghrelin-immunoreactive cells have been detected in tumors of the DES and, specifically, in well-differentiated endocrine tumors of the pituitary gland, gastroenteropancreatic tract, pancreas, and lung (27, 36, 53). Tumor cells also proved to express GHS receptor by reverse transcriptase–polymerase chain reaction analysis, suggesting a potential autocrine loop (27, 36).

Conclusions

Ghrelin is the most potent GHS so far discovered. Similar to GHS, it can act directly on the pituitary; however, the principal site of action is in the hypothalamus, where they can directly or indirectly synergize with GHRH. In addition to their endocrine effects, ghrelin and the GHSs are endowed with relevant extraendocrine effects that involve food intake and body weight control. These pharmacological properties may be relevant in defining the possible therapeutic use of ghrelin and the GHSs in the care of endocrine and extraendocrine pathological conditions.

Similar to other potent hormones, ghrelin is produced in specific cells of the DES of humans and various other

mammals. Its largest source is the ghrelin cell of the oxyntic stomach, in humans corresponding to the P/D_1 cell of previous classifications. Like other endocrine cells of the DES, ghrelin cells are present during early fetal life and in well-differentiated endocrine tumors. The presence of ghrelin cells in the DES indicates that, besides exerting a systemic hormonal role, ghrelin participates in the local functional control of the organs where it is located. Indeed, the ghrelin cell is another component of the complex brain-gut axis.

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