Ghrelin and Other Gastrointestinal Peptides Involved in the Control of Food Intake

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Abstract: The increasing prevalence of obesity has triggered intense research on its pharmacotherapy. Besides central neuroendocrine pathways, many peripheral endocrino-metabolic signals have been investigated, but only few are probably of some utility in weight loss. This review reports about ghrelin and other gastrointestinal peptides involved in hunger and satiety.

Key Words: Ghrelin, glucagon-like peptide 1, cholecystokinin, bombesin, (3-36) peptide YY.

GHRELIN

Ghrelin is a 28-amino acid acylated peptide predominantly produced by the stomach, although it is expressed also in the bowel, pancreas, kidney, lung, immune system, placenta, thyroid, testis, ovary, pituitary, and hypothalamus [1-3]. Ghrelin displays strong growth hormone (GH)-releasing activity mediated by the activation of the GH secretagogue receptor type 1a (GHS-R 1a). Prior to the discovery of ghrelin, this orphan receptor had been shown specific for a family of synthetic peptidyl and non peptidyl molecules known as GH secretagogues (GHS) [1,2,4]. GHS-Rs are concentrated in the hypothalamus-pituitary unit, but are also distributed in other central and peripheral tissues [1-4]. Apart from its potent GH-releasing action, ghrelin exhibits additional actions, including stimulation of prolactin and adrenocorticotrophic hormone (ACTH) secretion, negative influence on the gonadal axis, stimulation of appetite and positive influence on energy balance, modulation of endocrine and non-endocrine gastro-entero-pancreatic functions, cardiovascular actions and modulation of cell viability [1,5,6].

Circulating ghrelin levels are rapidly reduced by 80% after total gastrectomy, but gradually recover thereafter, indicating that the stomach is the major source of circulating ghrelin, but that other tissues can compensate for the loss of ghrelin production after gastrectomy [7].

Ghrelin is secreted a in pulsatile manner [8]. Notably, there is no strict correlation between ghrelin and GH levels, while ghrelin pulses are correlated with food intake and sleep cycles [8]. In humans as well as in animals, peaks in ghrelin levels anticipate food intake, suggesting that food intake is triggered by ghrelin [9].

Ghrelin secretion seems independent of age, at least from birth up to adulthood, although some decrease of ghrelin levels in elderly subjects has also been recently reported [10,11].

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In humans, ghrelin levels are increased by fasting and energy restriction and decreased by food intake and overfeeding [1,12]. Both oral and intravenous glucose loads inhibit ghrelin secretion in humans as well as in animals; on the other hand, free fatty acid as well as arginine load do not affect circulating ghrelin levels [13,14].

Evidence of a clear negative association between ghrelin and insulin secretion [12] suggested an inhibitory influence of insulin on ghrelin secretion, in agreement with data showing a direct modulation of the gastric ghrelin expression by insulin itself [15]. Indeed, during both euglycemic and hypoglycemic clamp the steady state increase in insulin levels is associated to a clear reduction in circulating ghrelin levels [16,17].

The most remarkable inhibitory input on ghrelin secretion is represented by the activation of somatostatin receptors by somatostatin as well as by its natural analogue cortistatin [18]. On the other hand, it has been reported that ghrelin stimulates somatostatin secretion in humans [19].

In all, evidence that insulin and somatostatin exert critical inhibitory actions on ghrelin secretion indicates that the latter is under major control from the endocrine pancreas that, in turn, is under ghrelin influence.

Among the different non-endocrine actions of ghrelin, an increasing attention has been focused on its role in the regulation of appetite and energy balance.

Years before ghrelin was discovered, different reports in rodents indicated that some GHS possess orexigenic activity [20,21,22]. In the last decade, a substantial amount of data showed that GHS were able to activate neurons in hypothalamic areas strictly involved in the control of energy balance [23-32]. Accordingly, ghrelin emerged as one of the most powerful orexigenic and adipogenic agents known so far [1,6,9,33]. At first, it was puzzling to link adipogenic effects to a hormone which was originally discovered as a potent secretagogue of GH, a lipolytic hormone, but progressively, ghrelin has emerged as a previously unidentified interface between energy balance regulation, glucose homeostasis, and hypothalamic neuropeptides [1,6,12,33].

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Ghrelin administration in rodents causes weight gain based on accretion of fat mass without changes in longitudinal skeletal growth and with a decrease of lean mass [34]. Ghrelin dose-dependently stimulate food intake in rodents, particularly after central administration [1,6,12,34,35].

Unlike other potent orexigenic agents (e.g., neuropeptide Y (NPY), Agouti-related protein (AgRP), melanin-concentrating hormone (MCH) that are active only when injected icv [36-38], ghrelin and synthetic GHS have orexigenic and adipogenic effects even after systemic administration [39]. The efficacy of ghrelin as orexigenic agent after peripheral administration would be explained by its transport across the blood brain barrier in blood-to-brain direction. However, hypothalamic areas playing a crucial role in the regulation of energy homeostasis, such as the ventromedial part of the arcuate nucleus, are not completely protected by the blood-brain-barrier [40]; these nuclei contain neurons expressing GHS-Rs [32] and might therefore mediate ghrelin effects [39,41].

It has been demonstrated that ghrelin influence on appetite and energy balance is at least partially mediated by hypothalamic neurons responsive to leptin [31,41-47].

Among the major hypothalamic pathways mediating ghrelin's influence on energy balance [43,44,46] one involves NPY-AgRP neurons [37,42], and the other involves the melanocortin receptors [48]. Ghrelin increases AgRP and NPY expression after both acute and chronic administration in rats [42,43, 46,49].

Thus, NPY and AgRP likely co-mediate ghrelin's effects on energy balance; NPY might be more important for acute effects, while AgRP might be involved in both chronic and acute ghrelin action in the hypothalamus [41]. However, other agents are likely involved in mediating the impact of ghrelin on appetite, food intake and energy balance; these include orexins, proopiomelanocortin (POMC), cocaine-amphetamine-related transcript (CART), MCH, ciliary neurotrophic factor (CNTF), GABA, galanin, corticotrophin releasing hormone (CRH) and somatostatin [41,45,50]. Besides the increase of appetite and food intake, reduced cellular fat oxidation would also contribute to increased fat mass induced by ghrelin as reported by some Authors [45].

It is noteworthy that ghrelin regulation of energy homeostasis seems mediated by efferent and afferent fibers of the vagal nerve [51]. In fact, intravenously administered ghrelin decreases the afferent activity of the gastric vagal nerve at low doses [51]. Moreover, the blockade of the gastric vagal afferent fibers abolishes ghrelin-induced feeding, GH secretion, and activation of NPY-producing and GH-releasing hormone (GHRH)-producing neurons in rats. Cholinergic influence on systemic ghrelin secretion has already been reported both in animals and in humans [52-54]. Nevertheless, cholinergic agonists and antagonists do not influence the endocrine response to ghrelin administration in humans [55].

It has been recently reported that desacyl-ghrelin, the main circulating form of ghrelin, decreased food intake and decreased gastric emptying [56]. The effects of desacyl-ghrelin require the existence of another receptor, most likely related to the motilin and ghrelin receptor, and they strengthen the concept of a family of peptides complementing each other in the regulation of appetite and motility [57].

Obviously, the effect of ghrelin in promoting food intake and modulating energy metabolism strongly suggested the possibility that ghrelin could be involved in the pathogenesis or in the metabolic and neuro-hormonal alterations commonly reported in obesity and in eating disorders and that ghrelin analogs acting as GHS-R agonists or antagonists could have a potential role in clinical practice.

Circulating ghrelin levels in obesity have been reported to be low, potentially representing a compensatory mechanism communicating to central regulatory centers that energy stores are sufficiently filled [58]. Notably, the reduced ghrelin secretion in obesity is restored by diet-induced weight loss, indicating that the inhibition of ghrelin secretion in obesity is only a functional impairment [58-60]. However, at present, the exact peripheral signals leading to a reduced ghrelin secretion in obesity have not been identified yet, although ghrelin gene polymorphisms have been described by several groups, linkage analysis studies failed however to prove a solid association between ghrelin and obesity [60-62].

While diet-induced human obesity, as well as polygenic (*e.g.* Pima Indians) or monogenic (*e.g.* MC4-R defect) causes of human obesity all present with low plasma ghrelin levels [59], severely obese patients with Prader-Willi syndrome show markedly increased plasma ghrelin levels [63]. The only other population where comparably high ghrelin levels have been reported are patients with cachexia or anorexia nervosa, where high ghrelin levels are believed to reflect a physiological compensation effort in response to either a chronically empty stomach or a markedly decreased fat mass [64]. PWS is the most frequent known cause of genetically induced obesity and is associated with a defect on the short arm of chromosome 15, while the exact pathogenetic mechanisms leading to the obesity syndrome in PWS remain unclear [65]. Apart from their adiposity, patients with PWS suffer from a severe hunger syndrome, decreased locomotor activity, impaired GH secretion, increased sleepiness and relative hypoinsulinemia [66,67]. Although it appears intriguing that hyperghrelinemia in PWS might be responsible, at least in part, for the majority of symptoms characterizing this disease, the biologic significance of the link between ghrelin and PWS remains at present unexplained [63].

Besides ghrelin hyposecretion, obesity is also a well known condition of impaired somatotroph function [68,69]. GH insufficiency in obesity reflects true impairment of GH production rate and has been demonstrated either in term of spontaneous secretion as well as in terms of somatotroph response to provocative stimuli [68,69]. The mechanisms accounting for this functional GH deficiency have not been fully elucidated so far and probably reflect neuroendocrine abnormalities, though a major role of peripheral hormones and metabolic factors has been more recently emphasized [68,69]. Accordingly, GH insufficiency in obesity has been reported to be reversed by long-term diet and marked weight loss, but is not restored by short term fasting [68,69].

Taking into account these activities, impaired ghrelin secretion and/or action had been theoretically predicted as having a role in such neuroendocrine alterations. In agreement with this hypothesis, food intake has been reported unable to suppress ghrelin levels in obese patients [14,58, 60,70,71].

In obese patients, ghrelin and synthetic GHS administration induce a remarkable increase in circulating GH levels (although 50% lower than in normal subjects), implying that the pituitary GH releasable pool is not exhausted [71-73]. This evidence does not support the hypothesis that ghrelin hyposecretion is fully responsible for GH insufficiency in obesity. The reduced GH response to ghrelin in obesity could be related to the concomitant hypoactivity of GHRH-secreting neurons as alterations in the hypothalamic somatostatinergic activity has not been definitely demonstrated in this clinical condition [68,69].

Therefore, although circulating ghrelin levels progressively decline with increasing BMI, data so far available do not support the existence of a causative relationship between ghrelin hyposecretion and hypoactivity in terms of GH releasing effect and hyposomatotropism in obesity and no definitive evidence exists that ghrelin analogues may represent in the next future a useful therapeutic tool in this pathologic condition.

Moreover, before considering potential clinical applications, a better knowledge on the physiology of the ghrelin system should be achieved. In fact, although since the acylated-ghrelin had been initially considered the only active ghrelin form [74], an increasing number of reports is showing that the unacylated form of ghrelin, which is unable to activate the GHS-R la and therefore to influence the endocrine pituitary function, exerts independent peripheral metabolic effects both *in vitro* [75,76] and *in vivo* [56,76,77] and modulates food intake [56,78], likely *via* still unknown different receptors. More recently, the complexity of this system has been further enriched by the isolation of obestatin, another gastric hormone derived from the same ghrelin gene, and able to decrease food intake, jejunal contraction, and body-weight gain in rats, likely acting *via* the orphan G protein-coupled receptor GPR39 [79]. Thus, in our present knowledge, two different peptide hormones, ghrelin and obestatin, seem to derive from the same gene and to exert opposite actions in weight regulation *via* the activation of distinct receptors. Notably, in one of them, ghrelin, posttranscriptional acylation leads to the synthesis of two distinct hormonal forms with at least partially different actions on metabolic functions and appetite control.

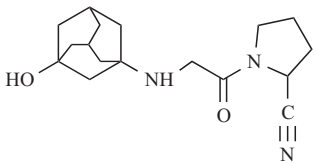
PRE-PROGLUCAGON GLP-1

Processing of the precursor pre-pro-glucagon is tissue specific resulting in different peptides: the pancreatic α-cells produce mainly the active hormone glucagon [80] whereas the intestinal L cells originate the glucagon-like peptides, GLP-1 and GLP-2 [81,82]. Glucagon enhances glycogenolysis and hepatic gluconeogenesis, while GLP-1 stimulates insulin secretion, inhibits gastric emptying and inhibits glucagon secretion. Recently, GLP-2 has been shown to be an intestinal growth factor and might be useful in the treatment of intestinal disease [83]. Focusing our attention on GLP-1 secreted by the endocrine intestinal L cells in response to meal ingestion, it seems that luminal lipids or carbohydrates strongly increase its secretion, but also neuroendocrine factors could play a role. In fact the response of its secretion is relatively rapid (*i.e.* between 5 and 30 minutes). Besides insulinotropic and glucagon suppressing effects, recent studies have shown that GLP-1 might also inhibit appetite and reduce food intake. Even after peripheral administration, GLP-1 can bind to receptors in the brain, specifically in areas with leaky blood brain barrier such as the subfornical region and the area postrema [84]. GLP-1 receptors are also expressed in several hypothalamus nuclei and are probably activated by GLP-1 producing neurons. Actually, central administration of GLP-1 in rats in fact inhibits food and water intake [85] with a specific effect (since it is prevented by GLP-1 antagonists), but also antagonizing the orexigenic effect of NPY [86]. This effect is dose-dependent and also long-lasting, making GLP-1 an interesting therapeutic tool for obesity (and also for diabetes mellitus) [87]. Notably GLP-1 receptor knockout mice do not overeat and do not become obese (similarly to NPY KO mice), conversely carboxypeptidase E –deficient fat/fat mice, characterized by a diminution of the processing of proglucagon leading to great reduction in GLP-1 levels, develop adult-onset obesity and diabetes mellitus [88]. Another enzyme of interest for potential therapeutic use of GLP-1 is the dipeptidyl peptidase IV (DPPIV), involved in the metabolic inactivation of GLP-1. Oral administration of a specific DPPIV inhibitor, isoleucine thiazolide, has been shown to improve glucose tolerance in obese Zucker rats [89]. Moreover, as expected, mice lacking DPPIV are protected against obesity and insulin resistance: indeed, pair-feeding and indirect calorimetry studies have suggested that reduced food intake and increased energy expenditure accounted for the resistance to high fat diet-induced obesity in DPPIV-/- mice [90].

Human studies have shown that obese subjects have an attenuated release of GLP-1 in response to oral carbohydrate but no difference was seen in response to oral fat load compared to normal controls [91]. Free fatty acids may inhibit carbohydrate-mediated GLP-1 secretion in human obesity, since heparin administration induces a fall of GLP-1 levels and acipimox administration induce a markedly higher GLP-1 response [92]. Test meal studies showed that i.v. GLP-1 infusion result in a prolonged period of reduced feeling of hunger (assessed by visual analog scale), with a slower rate of gastric emptying (as showed by acetaminophen test) [93,94]. Weight loss could partly restore GLP-1 secretion in response to meals [95]. Obese children (and also anorectic girl) show reduced GLP-1 levels after oral glucose tolerance test [96]. Moreover, GLP-1 augments insulin-mediated glucose uptake as demostrated by clamp studies in obesity [97]. Similar results are obtained with GLP-1 administration in diabetic subjects [98], in whom GLP-1 promotes satiety and reduces food intake, and recently it has been demonstrated that metformin significantly increases GLP-1 levels after an oral glucose load in obese nondiabetic subjects; this effect could be due to an inhibition of GLP-1 degradation [99].

Finally, increased GLP-1 levels, together with other anorexigenic intestinal peptides as cholecistokinin and peptide YY, have been observed 20 years after jejunoileal by-

pass for massive obesity, suggesting a role for those peptides in the maintenance of weight loss after bariatric surgery [100]. Long acting GLP-1 analogs (such as exendin-4 and liraglutide) have been investigated in recent years in clinical trials with convincing effects in improving glucose tolerance and in promoting weight loss [101]. DPPIV inhibitors (vildagliptin) share similar effects on glucose homeostasis (not on weight loss) and can be administered orally [101] (Fig. (**1**)).



VILDAGLIPTIN

Fig. (1). The structure of the DPPIV inhibitor vildagliptin.

CHOLECYSTOKININ

Cholecystokinin (CCK), in its three different circulating forms (CCK-8, CCK-22, and CCK-33), belongs to the gastrin family [102]. Gastrin and CCK release pancreatic glucagon from the alpha-cells of the pancreatic islets. CCK acts on the gallbladder causing it to contract and emptying it from bile. CCK increases bile flow and small and large bowel motility, causes the pyloric sphincter to contract and increases pancreatic enzyme secretion [102]. These effects are mediated *via* both CCKA and CCKB receptors. CCK is cleaved from pre-pro-CCK in the duodenum, upper jejunum (I-cells) and in the brain. The most important stimulus for CCK liberation is amino acids and fatty acids, which reach the duodenal mucosa. More than thirty years ago it was reported that [103] intraperitoneal injection of CCK reduces meal size in rats. Moreover, intraperitoneal administration of CCK was found to be more effective than intravenous administration [104], suggesting that action on the abdominal cavity is important for CCK modulation of feeding behavior. Subsequently, it was found that intact vagus nerve was necessary for CCK's effects on feeding, as they were lost in vagotomized rats [105].

CCK reduces the sensation of hunger probably with the inhibition of gastric emptying [106,107] and stimulating vagal afferent fibers sensitive to gastric distension that terminate in the brainstem. Evidence supporting this latter mechanism includes the finding that CCKA receptors are present on afferent vagus nerve fibers and that peripherally administered CCK requires an intact abdominal vagus nerve [108,109] to inhibit food intake. Gastric vagal afferents that are responsive to CCK terminate on cell bodies in the nucleus tractus solitarius [110], the primary brain area for processing afferent information from the gastrointestinal tract. Interestingly, it was found that obese rats (fa/fa Zucker rats) of both sexes had significantly higher CCK receptor binding levels in the hippocampus and in the midbrain in comparison to lean controls, demonstrating a correlation between genetic obesity and elevated CCK receptor binding levels in specific brain regions [111].

Another evidence of the short-term satiety effect of CCK was suggested by the finding that a CCK antagonist, proglumide, increases food intake in the rat [112]. Furthermore, it has been shown that brain concentration of this peptide is decreased in genetically obese mice as compared to non-obese animals [113]. As a neuropeptide, CCK could inhibit the serotoninergic system in "cafeteria-fed" and lean Sprague-Dawley rats and also the dopaminergic system in the Zucker strain [114]. Since peripheral CCK has a rapid, but short-lived effect on feeding behavior, it seems to represent a short term signal for energy balance. There is, however, evidence for a role in long term energy balance for CCK by its synergistic activity with insulin and leptin. In fact, the satiety induced by intraperitoneal CCK administration is potentiated by intracerebroventricular infusion of insulin [115] or systemic injection of leptin [116]. Long-term controllers of energy balance, therefore, may regulate adipose stores in part by modulating the sensitivity of short-term signals such as CCK [117].

Circulating CCK has been reported to be increased in obesity and, conversely, to be decreased in anorexia nervosa [118], but more relevant are the numerous reports stating that administration of CCK (both at pharmacological and physiological doses) decreases the size of test meal in lean and obese humans, suggesting that CCK may be useful in treating human obesity and bulimia [119-121]. In line with these findings, it was shown that [122] oral administration of a proteinase inhibitor II extracted from potatoes (POT II), which increases CCK release, significantly reduced energy intake of lean subjects. Another evidence of the satiety action of CCK was the utilization of loxiglumide, a CCKA receptor antagonist, that is able to largely prevent the inhibitory effect of intraduodenal fat on food intake mediated by the secretion of CCK [123].

As already reported, a recent study showed that fasting and postprandial CCK levels remained elevated 20 years after jejunoileal bypass [100]. However, CCK responses were not altered by gastric bypass or vertical banded gastroplasty [124]. Because the CCKA receptor mediates the anorexic effects of this neural and endocrine peptide, this receptor remains as a possible target in the treatment of obesity [125].

BOMBESIN

Bombesin is 14 aminoacid peptide that, similarly to CCK, was reported to reduce meal size in both normal and 'hypothalamically' obese rats, and even to lower body weight, when administered chronically [126]. It seems that the effect of bombesin on hunger is not mediated by the vagus nerve, since the satiety effect of CCK, somatostatin, and glucagon is abolished or markedly reduced by abdominal vagotomy, but this is not the case for bombesin [127]. Central administration of bombesin in the lateral ventricule lowers food intake [128], whereas its peripheral action could be mediated by a gastric mechanism inducing satiety, since anti-bombesin antibodies bind selectively to rat stomach [129]. Moreover the highest expression of bombesin receptors in the gastrointestinal tract is the gastric fund. The mechanism by which bombesin induces satiety is not com-

pletely understood: bombesin stimulates the release of CCK [130], so its action may be mediated partly *via* CCK secretion. In line with this hypothesis, rats lacking CCKA receptors, the so called Otsuka Long-Evans Tokushima Fatty (OLETF) rats, develop obesity, hyperglycemia, and non-insulin-dependent diabetes mellitus [131]. Intriguingly, these rats were completely resistant to exogenous CCK and their response to bombesin was attenuated.

Studies in humans show that [132] bombesin infusion inhibits food intake and increases satiety in lean women, whereas obese women are less sensitive to these bombesin-induced satiety effects [133].

(3-36) PEPTIDE YY

Peptide YY (PYY) is secreted from specialized endocrine cells (L cells) of the small and large bowel (primarily in the distal gastrointestinal tract). PYY is a member of the neuropeptide Y (NPY) family with a tyrosine residue at both C and N terminals, and shares also considerable homology with pancreatic polypeptide (PP). The main circulating form of PYY is (3-36) PYY [134], that has been shown to bind selectively to Y2 receptors (Y2R, member of the NPY receptor family). During fasting, circulating levels of PYY are suppressed, while after meals PYY is released into the circulation, within 15 minutes, with a peak in about one hour.

Peripheral administration of (3-36) PYY was initially reported to decrease high fat diet intake. Data in rodents show that prolonged administration is able to decrease weight gain [129]. The fact that (3-36) PYY is not able to inhibit food intake in Y2R-null mice has suggested that the anorectic effect requires the Y2R [135]. Peripheral administration of (3-36) PYY stimulates c-Fos expression within the arcuate nucleus and decreases hypothalamic NPY expression, whereas seems to increase the release of α-melanocyte concentrating hormone by activating POMC neurons. So the action of PYY could be exerted through inhibition of orexigenic NPY neurons and stimulation of anorexigenic POMC-neurons in the gut-hypothalamic circuit. Very recent data in mice show that PYY (that is co-secreted with GLP-1) has synergistic effects with exendin-4 (a GLP-1 analog) in reducing food intake [136].

Batterham and colleagues have demonstrated that infusion of this peptide in normal weight humans is also able to reduce 24-hour food intake [135]. Moreover, they showed that in obesity endogenous PYY levels are reduced, but the anorectic effect is preserved. In fact in a recent placebo-controlled study, PYY infusion decreased by about 30% the caloric intake in obese patients, similarly than in normal controls [137].

In 1997 a prospective bariatric surgery study [94] showed that 20 year after jejunoileal bypass fasting and postprandial PYY levels (and also motilin, CCK, neurotensin and GLP-1) were elevated compared to non-operated obese subjects. Moreover, a recent study [138] has shown that PYY concentration is lower in morbidly obese patients compared with non-obese controls and that after vertical band gastroplasty, PYY concentration gradually rises to the control levels. These two observations indicate that combined low levels of anorexigenic gastrointestinal peptides are involved in sustained obesity and that their increase could play a role in the weight loss induced by surgery.

CONCLUSIONS

The increased understanding of the mechanisms involved in food intake and in the pathogenesis of eating disorders could lead to the development of numerous anti-obesity agents. The improving knowledge on these gastrointestinal peptidergic systems has allowed to identify a large number of novel drug targets that could treat eating disorders or promote weight loss.

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