THE ROLE OF GHRELIN IN THE REGULATION OF FOOD INTAKE IN PATIENTS WITH OBESITY AND ANOREXIA NERVOSA

Ivana Dostálová[1,2] and Martin Haluzík[2]

[1]Institute of Endocrinology, Prague, [2]Third Department of Medicine, First Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic

Corresponding author:

RNDr. Ivana Dostálová, Ph.D.

3rd Department of Medicine, 1st Medical Faculty, Charles University

U Nemocnice 1

128 08 Prague 2

Czech Republic

Tel.: + 420224962908

Email: idostalova@centrum.cz

Short Title: Ghrelin in obesity and anorexia nervosa

Summary

Gastrointestinal hormones play an important role in the neuroendocrine regulation of food intake and postprandial satiety. Ghrelin is a 28-amino acid orexigenic peptide produced mainly by the stomach that is involved in both the long-term regulation of body weight and the short-term regulation of postprandial satiety. Impairments in ghrelin secretion may in concert with other factors play an important role in the development of both obesity and anorexia nervosa. Despite an intensive research the critical factors regulating physiological postprandial ghrelin response in healthy individuals and its modification by the presence of obesity and anorexia nervosa are only partially understood. The potential contribution of ghrelin to the differences of diet- vs. surgical-induced weight losses in morbidly obese patients is now also being recognized. The aim of this review is to summarize the current knowledge about the physiology and pathophysiology of ghrelin and to discuss its potential in the prevention and/or treatment of obesity and anorexia nervosa.

Key words: ghrelin • obesity • anorexia nervosa • macronutrients • obesity surgery

Introduction

The global increase in the prevalence of obesity and its associated comorbidities has stimulated intensive research focused on better understanding of energy metabolism regulation and the possibilities to prevent and/or treat obesity. Clustering of obesity with other pathologies such as arterial hypertension, dyslipidemia, hypercoagulation state and insulin resistance is commonly referred to as insulin resistance syndrome (Reaven 2006). Numerous large scale studies have demonstrated that the presence of insulin resistance syndrome markedly increases cardiovascular morbidity and mortality (Frayn and Coppack 1992).

The etiology of obesity is very complex and lies in the interplay of genetic and environmental factors. It has been suggested that decreased satiety perception represents an important risk factor for the development of obesity (Delgado-Aros *et al.* 2004). Obese subjects have delayed onset of satiety after meal consumption which might be due to alterations in hormonal responses to food intake (Schwartz and Morton 2002). Since existing therapeutic strategies to achieve and maintain clinically significant weight loss remain limited, modulation of satiety perception through the changes of gastrointestinal hormone (GI) secretion represents a promising approach to prevent and/or treat this disease and its complications (Le Roux and Bloom 2005).

On the other side of nutritional spectrum, paradoxical increase in the incidence of anorexia nervosa (AN) is alarming. The trend of modern societies that more slim means more success and unfavourable social conditions partly contribute to the initiation of this severe disorder. AN affects about 0.3% of young girls with a mortality of 6% / decade (Dardennes *et al.* 2007). Patients with AN are characterized by the abnormal eating behaviour and inadequate perception of body weight and numerous metabolic and endocrine abnormalities (Housova *et al*. 2005, Dolezalova *et al*. 2007). Patients with severe forms of AN suffer from chronic malnutrition (Casper 1996), however the exact etiopathogenesis of this disorder is

similarly as in obesity still unknown. Gut hormones have been under an intensive research as hot candidates on regulators of appetite and satiety in these patients.

The role of gastrointestinal hormones in the regulation of food intake

Complex physiological mechanisms have evolved to control food intake in mammals. For most people, the amount and composition of food eaten varies considerably from meal to meal and from day to day. Food consumption and ingested nutrients stimulate the release of a variety of hormones from enteroendocrine cells throughout the gut and pancreas. Most of these molecules have the potential to modulate food intake. GI hormone signalling results in three major outcomes: meal termination, inhibition of subsequent meal intake, and orexigenic modulation (Moran 2006). Overall, GI hormones constitute a significant part of the complex neuroendocrine regulation of energy balance. Most of GI tract hormones increase satiety and decrease food intake. The only known exception is a hormone ghrelin that has the opposite effects. Here we review the current knowledge about the physiology and pathophysiology of this hormone with special focus on its possible role in the etiopathogenesis of obesity and AN.

Ghrelin: physiology and pathophysiology

Ghrelin has been discovered by Kojima *et al.* (1999) as a natural ligand of the growth hormone (GH) secretagogue (GHS) receptor type 1a (GHS-R1a). Subsequently, ghrelin turned out to exert more pleiotropic actions, consistent with the widespread distribution of ghrelin and GHS-R expression in central and peripheral tissues. The GHS-R is highly expressed in the hypothalamus, including nucleus arcuatus, but is also found in the brainstem, pituitary, GI tract, adipose tissue and other peripheral tissues (Petersenn 2002).

Ghrelin is at present the only known GI hormone that increases food intake. Plasma ghrelin levels are inversely correlated with body weight and rise following weight loss in

humans (Cummings *et al.* 2002). The major source of circulating ghrelin is the stomach, although ghrelin mRNA and immunoreactivity are also found in other regions of the GI tract (Date *et al.* 2000). Ghrelin is composed of 28 amino acids with an acyl sidechain attached to the serine residue at position 3. This acyl group is crucial for ghrelin´s orexigenic and GH-releasing actions (Kojima *et al.* 1999). However, it has been suggested that desacylated ghrelin has other biological functions mediated by separate GHS-R subtypes (Baldanzi *et al.* 2002, Mackelvie *et al.* 2007, Giovambattista *et al*. 2008). The orexigenic effects of peripheral ghrelin are mediated via the central nervous system through activation neurons in the hypothalamic arcuate and paraventricular nuclei (Ruter *et al.* 2003, Janas-Kozik *et al.* 2007). The orexigenic effects of ghrelin are at least partially mediated via NPY and agouti-related protein (AgRP) (Nakazato *et al.* 2001, Chen *et al.* 2004). The recently described product of the ghrelin gene, named obestatin, was initially postulated to antagonize ghrelin orexigenic action in rats (Zhang et al. 2005). These initial findings were, however, disclaimed by the majority of later studies (Holst *et al.* 2007, Nogueiras *et al.* 2007, Yamamoto *et al.* 2007).

Considerable evidence implicates the role of ghrelin in mealtime hunger and meal initiation. Its circulating levels decrease with feeding and increase before meals, achieving concentrations sufficient to stimulate hunger and food intake (Cummings *et al.* 2001). Preprandial ghrelin surges occur before every meal on various fixed feeding schedules and also in individuals initiating meals voluntarily without time- or food-related cues. Ghrelin injections stimulate food intake rapidly and transiently, primarily by increasing appetitive feeding behaviours and the number of meals (Cummings 2006). Consistent with the prediction of ghrelin as a physiological meal initiator in humans, intragastric infusion of a glucose solution in rats and humans significantly suppresses plasma ghrelin levels, whereas intragastric infusion of the same volume of water does not suppress ghrelin (Tschop *et al.* 2000, Shiiya *et al.* 2002, Williams *et al.* 2003). However, non-caloric fibre reduces plasma

ghrelin to the same extent as a caloric mixed meal in healthy women (Nedvidkova *et al.* 2003).

The short-term overfeeding with high-fat diet in normal-weight healthy subjects reduces ghrelin levels, similarly as seen in obesity, suggesting that decreased ghrelin levels may precede the development of significant adiposity (Robertson *et al.* 2004). Weight loss induced by diet and exercise leads to a compensatory increase in circulating ghrelin in normal-weight healthy women. In these studies, changes in body weight, body composition and resting metabolic rate occured prior to changes in circulating ghrelin levels (Leidy *et al.* 2004).

The mechanisms controlling ghrelin secretion during fasting and postprandial suppression are unknown (Nakai *et al.* 2003). In healthy subjects, sham feeding (i.e., only chewing of meal without swallowing) decreases ghrelin levels to a similar extent as regular feeding, suggesting vagal involvement in the postprandial ghrelin fall (Arosio *et al.* 2004, Heath *et al.* 2004). The neural, but not the neurohumoral, branch of the sympathetic nervous system can directly stimulate ghrelin secretion (Mundinger *et al.* 2006).

Despite an intensive research it is still not completely clear what parts of digestive tract regulate ghrelin secretion. In some studies, neither gastric nor duodenal exposure to nutrients was required for nutrient-related suppression of ghrelin (Williams *et al.* 2003, Cummings 2006). Ghrelin secretion was rather the result of post-ingestive increases in jejunal osmolarity (information probably relayed to the foregut via enteric nervous signalling), as well as from insulin surges, respectively (Cummings 2006). However, it is conceivable that ghrelin suppression can be achieved equally by various different parts of the intestine coming in contact with nutrients (Overduin *et al.* 2005).

Specific effects of respective nutrients and caloric content of the meal on ghrelin levels still need to be clarified. In humans, the level of postprandial ghrelin suppression is proportional to ingested caloric load, but the recovery of plasma ghrelin is not a critical

determinant of intermeal intervals in healthy individuals (Callahan *et al.* 2004). In healthy subjects, a longer fasting period during the day, e.i., irregular meal pattern typical for several eating disorders, increases ghrelin concentration, but does not affect postprandial ghrelin response to a mixed meal (Briatore *et al.* 2006). Ghrelin suppression in healthy individuals depends on the macronutrient content of meals (Erdmann *et al.* 2003). Most studies have used mixed or carbohydrate-rich test meals, which clasically suppress ghrelin levels and measurements of hunger (Cummings *et al.* 2002, Shiiya *et al.* 2002, Callahan *et al.* 2004). Some authors have found that protein- and fat-rich meals increase ghrelin levels (Erdmann *et al.* 2003, 2004). In healthy humans, carbohydrates suppressed ghrelin to the greatest extent, whereas fat was the least effective (Monteleone *et al.* 2003). Glucose load inhibits ghrelin secretion after either oral or intravenous (iv) administration (Shiiya *et al.* 2002, McCowen *et al.* 2002, Nakagawa *et al.* 2002), whereas iv free fatty acid as well as arginin load does not affect circulating ghrelin levels in humans (Mohlig *et al.* 2002). Theoretically, weak suppression of ghrelin by ingested lipids could be one of the mechanisms underlying high-fat diet-induced weight gain (Astrup 2002).

Several studies focused on the possible role of insulin in the regulation of ghrelin levels. Although high doses of insulin, or combination of insulin and glucose reduced plasma ghrelin levels in some studies (Mohlig *et al.* 2002, Saad *et al.* 2002, Flanagan *et al.* 2003), other data from studies in insulin-deficient patients with type 1 diabetes indicate that increase in insulin levels after ingestion is not required for meal-related ghrelin suppression (Murdolo *et al.* 2003). Taken together, postprandial suppression of ghrelin in many studies goes in paralel with increase in glucose and insulin levels (Cummings *et al.* 2001, Tchop *et al.* 2001, Shiiya *et al.* 2002, Monteleone *et al.* 2003, Erdmann *et al.* 2004). However, the regulating role of insulin on postprandial ghrelin suppression is rather additive.

Ghrelin and obesity

Total and active fasting ghrelin levels are decreased in human obesity (Marzullo *et al.* 2006), which might represent a compensatory response to a sustained positive energy balance (Cummings and Shannon 2003). Among obese otherwise healthy adults plasma ghrelin concentrations are lower in more insulin resistant subjects relative to equally obese individuals with relatively higher insulin sensitivity (McLaughlin *et al.* 2004). Suppression of active form of ghrelin in obese during hyperinsulinemic-euglycemic clamp is inversely related to insulin resistance (St. Pierre *et al.* 2007). Obese subjects are not resistant to the effects of ghrelin administration (Cremonini *et al.* 2006) and ghrelin could play an important role in the endocrine abnormalities commonly present in obesity (Muccioli *et al.* 2002, Cummings and Shannon 2003). Obese people appear to be more sensitive to the appetite-stimulating effects of exogenous ghrelin than normal-weight subjects and inhibition of circulating ghrelin could be a useful therapeutic approach in the treatment of obesity (Druce *et al.* 2004). However, the effect of ghrelin administration on glucose and insulin levels is not direct and dose-dependent and its overall mechanism is still not completely clear (Alvarez-Castro *et al.* 2006, Tassone *et al.* 2003).

Some studies have shown a complete lack of postprandial ghrelin suppression in obese patients (English *et al.* 2002, Morpurgo *et al.* 2003, Moran *et al.* 2004). Other studies have found normal (Weigle *et al.* 2003, Romon *et al.* 2006) or incomplete (Greenman *et al.* 2004, Marzullo *et al.* 2006) postprandial ghrelin suppression in obese (Table 1). The postprandial ghrelin response in obese subjects is, in contrast to healthy individuals, independent of caloric content and macronutrient composition of the meal (Table 1). The reduced ghrelin response or its complete insensitivity to meal-induced suppression may contribute to the resistance to weight loss in some of obese patients (Greenman *et al.* 2004).

Studies focused on the effect of diet-induced weight loss on postprandial ghrelin responses have generally yielded inconsistent results (Weigle *et al.* 2003, Morpurgo *et al.* 2003, Moran *et al.* 2004, Romon *et al.* 2006) (Table 1). In some studies, weight loss restored some features of the normal regulatory role of ghrelin on hunger and meal initiation. It seems that particular amount of weight loss (more than 5 % of initial body weight) rather than duration of weight-reduction programme, is important for the restoration of postprandial ghrelin response (Table 1). Diet-induced weight loss preferentially improves plasma ghrelin response to a carbohydrate test meal in obese women (Romon *et al.* 2006), suggesting that the improvement in insulin sensitivity could play a role. Alterations in fat free mass with weight loss may also be involved in ghrelin regulation in obese subjects. Overall, changes in ghrelin levels could serve as an integrative signal reflecting changes in both fat and fat free mass to hypothalamic centers controlling energy homeostasis (Purnell *et al.* 2007).

While baseline ghrelin levels generally increase in response to diet-induced weight loss (Weigle *et al.* 2003, Romon *et al.* 2006) surgically-induced weight loss (e.g. gastric bypass) decrease ghrelin levels (Morinigo *et al.* 2004). It has been suggested that decreased ghrelin levels after obesity surgery may be involved in the mechanisms inducing sustained weight loss in contrast to more frequent relapses in obese patients with diet-induced weight loss.

It is also important to note that different surgical procedures are unequally effective in suppression of ghrelin. For example: Roux-en-Y gastric bypass (RYGBP) markedly suppresses fasting ghrelin levels in morbidly obese patients. The reduction of ghrelin after 6 weeks after RYGBP was described (Morinigo *et al.* 2004). Prolonged weight losses 9-31 months after RYGBP lead to further significant reduction of circulating ghrelin in obese patients (Cummings *et al.* 2002, Geloneze *et al.* 2003, Leonetti *et al.* 2003, Tritos *et al.* 2003). Paradoxical decrease in fasting plasma ghrelin after RYGBP surgery occures not only in patients with massive weight losses (Cummings *et al.* 2002, Geloneze *et al.* 2003), but also in

patients with weight loss comparable to those achieved by diet (Morinigo *et al.* 2004). These findings raise the possibility that this bariatric surgical procedure reduces weight at least in part by suppressing ghrelin production and its appetite-stimulating effects.

In contrast to gastric bypass prolonged weight loss 1 year after laparoscopical adjustable gastric banding results in a slight but significant rise in plasma ghrelin concentrations (Hanusch-Enserer *et al.* 2004, Leonetti *et al.* 2003). These findings are consistent with the hypothesis that suppression of ghrelin is one of the mechanisms explaining why gastric bypass can reduce body weight more effectively than gastric banding. Nevertheless, the mechanism by which gastric bypass leads to a reduction in ghrelin levels is still not completely clear. It has been suggested that a permanent absence of food in the empty stomach resulting from gastric bypass could cause a continuous stimulatory signal that ultimately suppresses ghrelin production through a process of overriding inhibition (Cummings *et al.* 2002). A modification in vagal control of fundus and anthrum cells of the stomach because of a gastric bypass procedure could be involved in paradoxical lowering of ghrelin production.

Another obesity surgery procedure sleeve gastrectomy markedly suppresses ghrelin levels probably due to resection of gastric fundus the most important site of ghrelin production in humans (Langer *et al.* 2005, Kotidis *et al.* 2006). The reduction of ghrelin levels after sleeve gastrectomy remains stable at follow-up 6 months postoperatively, which may contribute to the superior weight loss after this procedure when compared with gastric banding (Langer *et al.* 2005).

Ghrelin and anorexia nervosa

Fasting ghrelin levels are elevated in both restrictive and binge/purge form of AN and return to normal levels after partial weight recovery (Otto *et al.* 2001, Tanaka *et al.* 2003,

Misra *et al.* 2005, Nakahara *et al.* 2007) or even overburst to values lower than in controls after 3-6 months of realimentation therapy (Janas-Kozik *et al.* 2007). High ghrelin levels in AN appear to be a compensatory mechanism to increase caloric intake and induce a state of positive energy balance. Both body mass index and the binge-eating/purging behavior influence fasting ghrelin levels in patients with AN (Tanaka *et al.* 2003, Troisi *et al.* 2005, Janas-Kozik *et al.* 2007). Reduced food intake in patients with AN despite chronically increased ghrelin levels thus could reflect a decreased sensitivity to ghrelin effects (Misra *et al.* 2005). Several studies have shown that patients with AN are less sensitive to ghrelin administration in terms of GH response and appetite than healthy women (Broglio *et al.* 2004, Miljic *et al.* 2006). Postprandial ghrelin levels in patients with AN remain high after consumption of a 585 kcal solid mixed meal (32.6 g fat, 17.6 g protein, 50 g carbohydrate) and do not fall even two hours after meal consumption (Nedvidkova *et al.* 2003), whereas 250 ml fluid meal of 250 kcal (8.3 g fat, 9.4 g protein, 34.4 g carbohydrate) (Otto *et al.* 2005) as well as a 400 kcal standard test meal (Nakahara *et al.* 2007) suppresses plasma ghrelin in patients with AN. Based on the yet published data, it can not be clearly concluded whether the postprandial ghrelin response in AN depends on caloric content, total volume or macronutrient composition of a meal. Suppressive effect of glucose on active (octanoylated) ghrelin secretion is preserved in adult patients with AN (Nakai *et al.* 2003, Hotta *et al.* 2004, Harada *et al.* 2008), but not in adolescent girls with AN (Misra *et al.* 2004). Ghrelin response to glucose administration in patients with AN also depends on insulin sensitivity and eating behavior (Tanaka *et al.* 2003).

The changes of ghrelin concentrations in obesity are opposite to those in AN, suggesting that ghrelin is a good marker of nutritional status (Soriano-Guillen *et al.* 2004). The lack of suppression of ghrelin secretion after a meal may be a critical factor in the pathophysiology of both obesity and eating disorders. Abnormalities in the release of ghrelin or insensitivity to its

effects may be involved in alterations of food intake in both obesity and anorexia nervosa (Date *et al.* 2005).

Summary

Ghrelin, a gut hormone with orexigenic effect, is markedly increased in patients with AN and significantly reduced in obese subjects. The secretion of ghrelin in stomach is stimulated by the combination of neural (vagus), mechanical (distension), chemical (osmolarity; caloric content and macronutrient composition of the meal) and hormonal (insulin) factors with unknown priority. The expected levels of fasting total plasma ghrelin levels are more than 1000 pg/ml in patients with AN, less than 400 pg/ml in obese subjects and in a range of 400-1000 pg/ml in healthy normal-weight subjects. Postprandially, ghrelin levels are suppressed in dependence of caloric content and macronutrient composition of the meal in healthy subjects. In both obese and AN patients, the postprandial ghrelin response is partly or completely lacking and it is independent of the caloric content and macronutrient composition of the meal.

Conclusion and perspectives

Efforts to develop pharmacological treatments for obesity have increased tremendously in the last decade, spurred by the increase of obesity prevalence and its recognition of as a chronic disease with severe consequences and complications (World Health Organization, 1998). More efficient drugs are still required to combat the obesity epidemic.

Gut peptides have received growing attention for their ability to regulate many GI functions, particularly those related to food intake and digestive motility (Gourcerol and Tache 2007). In contrast to the current medicaments that affect systems relatively indiscriminately, the use of gut hormones as therapeutic agents would have the advantage of

targeting only the relevant appetite control systems. It seems likely that permanent weight loss will reguire continuous treatment throughout the life of a patient, or at least for extended periods of time.

Ghrelin´s prokinetic and orexigenic effects have opened new potential therapeutic venues for the modulation of food intake (Klok *et al.* 2007). At present, ghrelin is the only peripheral orexigenic signal effective after i.v. injection and/or chronic peripheral administration (Tschop *et al.* 2000, Wren *et al.* 2001). Thus, ghrelin itself may be useful orexigenic agent for the treatment of disorders accompanied by chronic malnutrition due to decreased food intake such as AN. Blocking or neutraliziation of the orexigenic action of ghrelin could be, on the other side, a reasonable approach to decrease an excessive food intake in obesity. However, it should be noted, that appetite is regulated by numerous factors that may interact with and compensate for each other. Therefore the effectiveness of such approach has to be directly shown in clinical studies. Further research is required to investigate whether ghrelin antagonists/agonists might be viable antiobesity/malnutrition-treating drugs that can be used in wide clinical practice.

Acknowledgements: Supported in part by MZO 000064165.

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Table 1. Postprandial response of total ghrelin in obese patients

Postprandial ghrelin response before weight loss	Test meal (caloric value, macronutrient composition)	Weight-reduction programme (duration, daily caloric value, % of daily energy in macronutrients)	Average weight loss (percent of initial weight)	Postprandial ghrelin response after weight loss	Study
×	714 kcal 57% C, 12% P, 31% F	no	-	-	English 2002
×	550 kcal 48% C, 33% F, 19% P	3 wk 1200-1800 kcal/day 21% P, 53% C, 26% F	5.6%	=	Morpurgo 2003
×	646 kcal 31% P, 14% F, 55% C	12 wk 1435 kcal/day 30% P, 40% C, 30% F	7.5%	↓	Moran 2004
×	646 kcal 11% P, 15% F, 76% C	12 wk 1435 kcal/day 55% C, 15% P, 30% F		↓	
↓	-	12 wk ad libitum 15% F, 65% C, 20% P	5%	=	Weigle 2003
↓ shorter	300 kcal 75 g of dextrose	no	-	-	Greenman 2004
↓	400 kcal 91% F, 5,5% C, 4.5 % P				
↓	240 kcal 84% P, 5% C, 11% F				
↓	813 kcal 79% F, 18% P, 3%	7 wk 800 kcal/day 20% C, 50% P, 30% F	10.5%	=	Romon 2006
↓	813 kcal 81% C, 18% P, 1% F			↓↓	

↓ < 13%	500 kcal 53% C, 30% F, 17% P	no	-	-	Marzullo 2006
↓ < 14%	500 kcal 28% C, 55% F, 17% P				
↓ < 16%	500 kcal 45% C, 25% F, 30% P				

C = carbohydrates, F = fat, P = protein
× lack of suppression seen in healthy controls; ↓ postprandial suppression; ↓↓ greater suppression than before weight reduction; = the same postprandial response as before weight reduction; ↓ < 15% supression, but about 15% less than in healthy controls