Obestatin: An Interesting but Controversial Gut Hormone

Antonio Lacquaniti^a Valentina Donato^a Valeria Chirico^b Antoine Buemi^a
Michele Buemi^a

Departments of ^aInternal Medicine and ^bPediatric Sciences, University of Messina, Messina, Italy

Key Words

Obestatin • Food intake • Obesity • Diabetes mellitus • Cancer

Abstract

Obestatin is a 23-amino acid peptide hormone released from the stomach and is present not only in the gastrointestinal tract, but also in the spleen, mammary gland, breast milk and plasma. Obestatin appears to function as part of a complex gut-brain network whereby hormones and substances from the stomach and intestines signal the brain about satiety or hunger. In contrast to ghrelin, which causes hyperphagia and obesity, obestatin appears to act as an anorectic hormone, decreasing food intake and reducing body weight gain. Further studies have shown that obestatin is also involved in improving memory, regulating sleep, affecting cell proliferation, increasing the secretion of pancreatic juice enzymes and inhibiting glucose-induced insulin secretion. This hormone has not only been studied in the field of physiology but also in the fields of obesity and diabetes mellitus, and in patients with psychogenic eating disorders. Obestatin has a role in regulating the cell cycle by exerting proliferative effects that may be seen in cell physiology and

oncology. Given the current controversy regarding the effects of obestatin and its cognate ligand, this article provides the latest review of the physiological and pathological characteristics of this hormone.

Copyright © 2011 S. Karger AG, Basel

Introduction

The word obestatin is a contraction of obese, and derives from Latin 'obedere', meaning 'to devour' and 'statin', denoting suppression. It is a 23-amino acid peptide hormone that is derived from post-translational cleavage of preproghrelin, the same peptide precursor as ghrelin, which is a 28-amino acid peptide released from the stomach [1] (fig. 1). Ghrelin is involved in energy homeostasis and has orexigenic properties, inducing a short-term increase in food consumption, a positive energy balance and an increase in fat deposition. Two major molecular forms are found in plasma: acylated ghrelin and des-acyl ghrelin. The former is the biologically active form of ghrelin and recent findings indicate that at least part of the octanoate for this acylation is derived from dietary fat.

Fig. 1. Post-translational processing of preproghrelin to mature obestatin and ghrelin.

Ghrelin O-acyl transferase is essential for ghrelin acylation and this process is also derived from dietary fat. In fact, Kirchner et al. [2] have proposed that the ghrelin O-acyl transferase-ghrelin system acts as a nutrient sensor by using readily absorbable medium-chain fatty acids to signal to the brain that high caloric food is available, leading to optimization of nutrient partitioning and growth signals. Although ghrelin is often called a hunger hormone, recent findings indicate that its physiological function is not to stimulate eating, but rather to prepare the organism for the arrival of nutrients. In fact, Liu et al. [3] demonstrated that acylated ghrelin levels rise before a meal and drop afterwards, while plasma concentrations of acyl ghrelin do not increase under conditions of prolonged fasting, thus suggesting a role as hunger signal for ghrelin. Gronberg et al. [4] found that the subcellular localization of obestatin and ghrelin is essentially identical, indicating that obestatin and ghrelin are stored in the same secretory vesicles. Obestatin is present not only in the gastrointestinal tract, but also in the spleen, mammary gland, breast milk and plasma [5]. It is also conserved in the preproghrelin sequences of 11 different mammalian species and the predicted sequence of obestatin, as well as ghrelin, is identical in rats and mice

[6]. Thus, there is ample evidence that obestatin plays a key role in metabolic processes common to all these different species, including humans.

Obestatin Receptor

While the receptor through which ghrelin exerts its actions is well-established, there are conflicting opinions as to the type of receptor for obestatin. Zhang et al. [7] reported that obestatin is the cognate ligand for the G protein-coupled receptor-39 (GPR39). Treatment with obestatin induced c-fos expression in wild-type mice, but not GPR39 null, thus providing further support for the ligand-receptor relationship between obestatin and GPR39 [8]. Recent reports indicate that obestatin is unlikely to be the endogenous ligand for GPR39. Chartrel et al. [9] provided independent evidence that obestatin does not interact with GPR39, observing no effects of obestatin on GPR39-transfected cells in various functional assays. In a study of GPR39 knockout mice, it was concluded that GPR39 may not be the obestatin receptor. Furthermore, Granata et al. [10] reported that obestatin promotes beta-cell and human islet survival by binding to glucagon-like peptide-1 receptor (GLP-1R), the receptor through which incretins act. Similarly, incretins also reduce gastrointestinal motility with a paracrine peripheral action and induce satiety and reduce food intake in the (hindbrain) specifically in the postrema and nucleus of the solitary tract) [11, 12]. To date, the receptor for obestatin remains unknown and further studies are required to reveal the exact relationship between obestatin, GPR39 and GLP-1R.

Physiological Functions of Obestatin

Very little is known about the physiological role of obestatin in humans. It appears to function as part of a complex gut-brain network whereby hormones and substances from the stomach and intestines signal the brain about satiety or hunger. However, the question arises as to when obestatin is synthesized. Obestatin secretion is pulsatile and displays an ultradian rhythmicity, in a similar way to ghrelin and GH secretion, but plasma ghrelin and obestatin levels are not strictly correlated and the number of obestatin pulsatile episodes may seem slightly lower than that observed for ghrelin and GH secretion [13]. In contrast to ghrelin, obestatin appears to act as an anorectic hormone, decreasing food intake, slowing gas-

Table 1. Physiological actions of obestatin

Apparatus	Effects	Ref.
Gastrointestinal system	Decrease food intake, slow gastric emptying, reduce jejunal motility, reduce body weight Increase the secretion of pancreatic juice enzymes Inhibit glucose-induced insulin secretion	[14] [20] [21]
Central nervous system	Improve memory and explicate an anxiolytic action Regulate sleep Inhibitory effects on water drinking	[15] [16] [26]
Hormone secretion	Not modify GH and corticosterone secretion No effects on plasma PRL, ACTH and TSH levels Decrease plasma vasopressin levels but not oxytocin levels No influence on serum leptin levels	[13] [25] [26] [7]
Cell proliferation	Induce cell proliferation in cultures of human retinal pigment epithelial cells Induce ovarian cell proliferation, apoptosis and secretion	[17] [18]

tric emptying and jejunal motility, and reducing body weight gain in rodents [14]. However, additional studies have, in fact, shown that obestatin is involved in improving memory [15], regulating sleep [16], affecting cell proliferation [17–19], increasing the secretion of pancreatic juice enzymes [20], promoting survival of pancreatic B cells [10] and inhibiting glucose-induced insulin secretion [21]. It is also possible that circulating obestatin acts on central nervous system targets by crossing the blood-brain barrier (BBB). While human ghrelin, as described by Banks et al. [22], possesses a moderate but specific saturable transport system to permeate the BBB in mice, Pan et al. [23] demonstrated that obestatin does not have specific uptake by endothelial cells in the BBB. It is worth noting that areas of the brain, such as the hypothalamic arcuate nucleus which regulate hunger, are not surrounded by the BBB. Another important aspect that has been studied by various authors is the role of obestatin in the regulation of hormone secretion in vitro and in vivo. Bresciani et al. [24] found that in vivo obestatin does not modify GH and corticosterone secretion. Yamamoto et al. [25] demonstrated that in anesthetized male rats administration of obestatin did not show any effects on plasma GH, PRL, ACTH and TSH levels. Samson et al. [26] discovered that obestatin exerted significant inhibitory effects on water drinking after intracerebroventricular administration in rats in response to dehydration and angiotensin II (Ang II) administration. In a subsequent work, they demonstrated that obestatin, in response to both pharmacologic and physiologic stimuli, reduces the secretion of vasopressin (AVP) in the brain and hypothesize that the complementary actions of obestatin in in-

hibiting thirst and AVP secretion reflect a physiologically relevant action of the endogenous peptide to buffer total body fluid content [27] (table 1). It must be considered that there is substantial evidence that in various conditions, obestatin fails to reproduce the anorexigenic property initially reported. Nogueiras et al. [28] did not observe any effect of obestatin on food intake, body composition, energy expenditure, locomotor activity, respiratory quotient, or hypothalamic neuropeptides involved in energy balance regulation. Moreover, subsequent studies have demonstrated that obestatin does not activate the GPR39 receptor and, in light of this controversy, it has also been proposed that obestatin be renamed as ghrelin-associated peptide.

Pathological Involvement of Obestatin

Obestatin has not only been studied in the field of physiology. Since its discovery, the relationship between obestatin and disease has been investigated particularly in the field of obesity, diabetes mellitus and in patients with psychogenic eating disorders. In recent years, many works regarding this peptide have been published and it has also been studied in different syndromes, other than those in the field of obesity and metabolic and energetic effects (table 2).

Obestatin and Obesity

Studies in humans have shown that plasma obestatin levels are significantly lower in obese subjects, as compared to lean controls, indicating a role for obestatin in

Table 2. Obestatin and diseases

Disease	Effects	Mechanisms	Ref.
Type 2 diabetes mellitus	At a low glucose concentration, obestatin potentiated the insulin response to glucose At a high glucose concentration, obestatin inhibited the insulin release	At a high glucose concentration, the beta cells are less responsive to obestatin than at a normal glucose level, and the glucose concentration bathing the beta cell appears to be a critical factor for the insulinotropic activity of obestatin	[39]
Atherosclerosis	Obestatin decreased vascular cell adhesion molecule-1 (VCAM-1) expression in endothelial cells Obestatin increased oxidized low-density lipoprotein binding to macrophages	Reducing the expression of VCAM-1 confers an anti-atherogenic role to obestatin Obestatin can lead to lipid accumulation and foam cell formation and eventually into fatty streak formation in the arterial wall leading proatherogenic properties	[41]
Anorexia nervosa (AN)	Patients with AN have higher plasma obestatin	In underweight AN subjects, an enhanced expression of the preproghrelin gene leads to an enhanced production of obestatin	[32]
Cancer	Obestatin-induced cell proliferation	The action of obestatin was induced by mitogen-activated kinase kinase/extracellular signal-regulated kinases1/2 (ERK1/2) phosphorylation	[19]

long-term body weight regulation [30]. Zamrazilová et al. [31] observed that lower plasma obestatin levels were found in obese subjects compared with women of normal weight and anorexic patients. In human subjects with anorexia nervosa or obesity, plasma obestatin correlated negatively with body mass index (BMI), leptin, insulin, glucose, and homeostasis model assessment insulin resistance (HOMA-IR), but was positively correlated with acyl-ghrelin and desacylghrelin. This suggests that basal secretions of obestatin and ghrelin may be regulated in a similar manner, being influenced together by adiposity and insulin resistance [32]. Mafra et al. [33] described lower plasma obestatin concentrations in patients on hemodialysis with a body mass index higher than 23, with this inverse correlation that could probably be an expression of insensitivity to the action of this anorectic factor in uremic patients. Lacquaniti et al. [34, 35] also studied obestatin in dialysis and renal transplant patients and highlighted lower plasma obestatin levels in these subjects and its inverse correlation with BMI.

Obestatin has not only been studied in adult but has also been associated with obesity in childhood. Zou et al. [36] investigated the effects of obestatin on obesity in children by measuring fasting obestatin and ghrelin/obestatin ratio. The result was that fasting plasma levels of obestatin tended to decrease. It is important to emphasize that in this work, the ghrelin/obestatin ratio in obese

children was significantly lower, not higher, than that in controls, in contrast to the study of ghrelin/obestatin in adults. Butler and Bittel [37] measured plasma obestatin and ghrelin levels in Prader-Willi syndrome (PWS), an obesity syndrome characterized by rapid weight gain and excessive food intake, establishing that obestatin was higher in infants with PWS compared to control infants.

Obestatin and Diabetes Mellitus

The role of obestatin in the pathophysiology of diabetes mellitus is based on several studies in vivo that have shown the influence of obestatin on pancreatic hormone secretion. There is also evidence of fluctuation of pancreatic insulin releases in vitro after administration of obestatin and glucose. In vitro, there were different results based on the concentration of glucose used in different protocols as a stimulus on pancreatic cells. Qader has found that, in isolated beta-islets from mouse and rat pancreas, maintained at a constant glucose level, obestatin inhibits insulin [38]. On the other hand Granata et al. [10] demonstrated that obestatin increases insulin secretion, in both the absence of or at a low glucose concentration. Egido et al. [39] concluded that obestatin exerts a dual effect on glucose-induced insulin secretion: at a low concentration, it potentiated the insulin response to glucose, while at a high concentration, it inhibited the insulin release evoked by this stimulus. This finding clearly indi-

cates that at a high glucose concentration, beta cells are less responsive to obestatin than at a normal glucose level, and that the glucose concentration bathing the beta cell appears to be a critical factor for the insulinotropic activity of obestatin. In vivo, Fontenot et al. [40] studied a particular physiological condition: pregnancy. It is an interesting metabolic state because it involves a short-term weight gain during which the possibility of concurrent gestational diabetes may occur, but it is normally accompanied by a large weight loss and euglycemia immediately after birth. The concentration of obestatin circulating in the blood was significantly lower in obese and obese diabetic pregnant women compared to controls.

Obestatin and Atherogenesis

Atherosclerosis is characterized by endothelial dysfunction, lipoprotein oxidation, leukocyte infiltration, release of various chemotactic and growth factors. Low-grade inflammation is known to be associated with obesity and also with the initiation and progression of vascular atherosclerosis. Several studies in humans and animal models have exhibited both beneficial effects of ghrelin in the cardiovascular system, such as a gain in left ventricular mass, an increase in left ventricular ejection fraction and correlation with atherosclerosis, demonstrating its important regulatory role in cardiovascular homeostasis. Few works have involved the study of obestatin in the field of atherosclerosis and regulation of blood pressure. Kellokoski et al. [41] demonstrated in vitro that obestatin decreases vascular cell adhesion molecule-1 (VCAM-1) expression in endothelial cells when stimulated with tumor necrosis factor- α (which stimulated monocyte adhesion) and increases oxidized low-density lipoprotein (Ox-LDL) binding to macrophages. Reducing the expression of endothelial adhesion molecules like VCAM-1 confers an anti-atherogenic role to obestatin, while an increase in Ox-LDL uptake by macrophages leads to lipid accumulation and foam cell formation and eventually into fatty streak formation in the arterial wall leading to proatherogenic properties. Ozbay et al. [42] demonstrated slightly higher concentrations of saliva ghrelin and obestatin in subjects with ischemic heart disease compared with control groups, suggesting that the two peptides can participate directly in the regulation of energy metabolism in ischemic heart tissue. Obestatin may also have a potential role in the regulation of blood pressure, as demonstrated by Ren et al. [43] who found that there is a positive correlation between plasma obestatin concentration and mean arterial pressure in

Fig. 2. Obestatin-stimulated signaling pathway during ERK 1/2 activation in cells. Obestatin activates a PI3K that results in the phosphorylation of PKC- ϵ which would activate Src. The latter would activate Raf-dependent ERK 1/2 activation via Ras or by a direct activation of Raf. After activation, ERK 1/2 are translocated to the nucleus, where they phosphorylate and activate transcription factors that lead to the mitogenic activity promoting G₁ > S progression. PI3K = Phosphoinositide 3-kinase; PKC- ϵ = protein kinase C; Raf = serine/threonine kinase; ERK = extracellular signal regulated kinases.

normal pregnant women and pregnant women with pregnancy-induced hypertension. Further in vitro and in vivo studies will certainly be required in order to establish the proper relationship between obestatin, lipid metabolism and the early stages of the process of atherogenesis in the cardiovascular system.

Obestatin in Physiological and Neoplastic Cell Proliferation

Different studies have shown that obestatin has a role in regulating the cell cycle by exerting proliferative effects and this is evident both in cell physiology and in oncology. Zhang et al. [8] spotlight the ability of obestatin to induce early-response gene expression c-fos and the activation of the ERK and MAPK pathway in the stomach, intestine, liver and kidney using cultured preadipocytes. The mechanisms of cell proliferation are shown in figure 2. Camiña et al. [17] evaluated the effect of obestatin on

cell proliferation in primary cultures of human retinal pigment epithelial cells. The results showed that this peptide induced cell proliferation in a dose-dependent manner with MEK/ERK 1/2 phosphorylation. Obestatin induces the association of GPR39/beta-arrestin 1/Src signaling complex resulting in the transactivation of the epidermal growth factor receptor and downstream Akt signaling [44]. Mészárosóvá et al. [18] investigated a role of obestatin in the direct control of porcine ovarian cell proliferation, apoptosis and secretion. Obestatin enhances the expression of several markers of proliferation (peptides PCNA, cyclin B1 and MAP kinase), which are involved in the promotion of the mitotic phase of the cell cycle. Obestatin can also inhibit expression of cell proliferation markers through stimulation of p53, known blocker of cell cycle. Granata et al. [10] claimed that obestatin binds GLP-1 receptors on pancreatic β -cell lines and human islets and induces β -cell survival and proliferation through GLP-1 receptor-mediated mechanisms, as well as downstream responses including the phosphorylation of ERK1/2 and Akt. The effect of obestatin in two neuroendocrine tumor cell lines has been investigated by Volante et al. [45], underlining the proliferative effects of obestatin. Obestatin activates cell proliferation in the gastric cancer cell line KATO-III inducing cell proliferation by mitogen-activated kinase kinase/extracellular signal-regulated kinases1/2 (ERK1/2) phosphorylation [19]. However, it should be noted that there are works in the literature that underline that obestatin also has antiproliferative effects. In a study by Iglesias et al. [46], obestatin did not modify the cell cycle or viability of the murine cardiomyocyte cell line HL-1, and was not able to prevent cytosine arabinoside-induced apoptosis of HL-1 cardiomyocytes. In a work conducted by Zhang et al. [47] it was demonstrated that obestatin can inhibit the proliferation and differentiation of 3T3-L1

preadipocytes. Obestatin involvement in carcinogenesis was highlighted by Alnema et al. [48] who examined the immunohistochemical features of oral squamous cell carcinoma in relation to the tissue concentration of ghrelin and obestatin. Expression of ghrelin and obestatin was decreased or absent in relation to the invasiveness of the carcinoma with a hypothetical role of these two peptides in the coordination of normal cell division, tumor growth and metastasis.

Conclusions

Obestatin is a hormone linked to the regulation of appetite in humans reducing food intake, body weight gain, gastric emptying and suppression of intestinal motility and it could be a useful marker of the nutritional status reflecting adiposity and insulin resistance.

There are several works underlying the intestinal hormonal network complexity [49, 50], but most works have given greater importance to ghrelin rather than obestatin. However, as studies have progressed, many disputes on the physiological function of obestatin have emerged; this review has dealt with all these different points of view.

Our work reviews all aspects of this hormone, underlying its role in the pathophysiology of diabetes mellitus with the influence of this peptide on pancreatic hormone secretion, in the process of atherogenesis, obesity, in the regulation of cell cycle exerting proliferative effects both in cell physiology and in oncology.

Further experiments are needed to clarify the role of obestatin and its receptor in order to consider it as an endocrine marker that could reflect the changes of acute and chronic nutritional status, but also to make obestatin a potential leading drug against obesity.

References

- 1 Zhao CM, Furnes MW, Stenstrom B, et al: Characterization of obestatin- and ghrelin-producing cells in the gastrointestinal tract and pancreas of rats: an immunohistochemical and electron-microscopic study. *Cell Tissue Res* 2008;331:575–587.
- 2 Kirchner H, Gutierrez JA, Solenberg PJ, et al: GOAT links dietary lipids with the endocrine control of energy balance. *Nat Med* 2009;15:741–745.
- 3 Liu J, Prudom CE, Nass R, et al: Novel ghrelin assays provide evidence for independent regulation of ghrelin acylation and secretion in healthy young men. *J Clin Endocrinol Metab* 2008;93:1980–1987.
- 4 Gronberg M, Tsolakis AV, Magnusson L, et al: Distribution of obestatin and ghrelin in human tissues: immunoreactive cells in the gastrointestinal tract, pancreas, and mammary glands. *J Histochem Cytochem* 2008; 56:793–801.
- 5 Aydin S, Ozkan Y, Erman F, et al: Presence of obestatin in breast milk: relationship among obestatin, ghrelin, and leptin in lactating women. *Nutrition* 2008;24:689–693.
- 6 Gualillo O, Lago F, Casanueva FF, et al: One ancestor, several peptides post-translational modifications of preproghrelin generate several peptides with antithetical effects. *Mol Cell Endocrinol* 2006;256:1–8.

- 7 Zhang JV, Ren PG, Avsian-Kretchmer O, et al: Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. *Science* 2005;310:996–999.
- 8 Zhang JV, Jahr H, Luo CW, et al: Obestatin induction of early-response gene expression in gastrointestinal and adipose tissues and the mediatory role of G protein-coupled receptor, GPR39. *Mol Endocrinol* 2006;22:1464–1475.
- 9 Chartrel N, Alvear-Perez R, Leprince J, et al: Comment on 'Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake'. *Science* 2007;315:766.
- 10 Granata R, Settanni F, Gallo D, et al: Obestatin promotes survival of pancreatic beta-cells and human islets and induces expression of genes involved in the regulation of beta-cell mass and function. *Diabetes* 2008;57:967–979.
- 11 Yamamoto H, Kishi T, Lee CE, et al: Glucagon-like peptide-1-responsive catecholamine neurons in the area postrema link peripheral glucagon-like peptide-1 with central autonomic control sites. *J Neurosci* 2003;23:2939–2946.
- 12 Holst JJ: The physiology of glucagon-like peptide 1. *Physiol Rev* 2007;87:1409–1439.
- 13 Zizzari P, Longchamps R, Epelbaum J, et al: Obestatin partially affects ghrelin stimulation of food intake and growth hormone secretion in rodents. *Endocrinology* 2007;148:1648–1653.
- 14 Ariysu H, Takaya K, Tagami T: Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. *J Clin Endocrinol Metab* 2001;86:4753–4758.
- 15 Carlini VP, Schioth HB, Debarioglio SR: Obestatin improves memory performance and causes anxiolytic effects in rats. *Biochem Biophys Res Commun* 2007;352:907–912.
- 16 Szentirmai E, Krueger JM: Obestatin alters sleep in rats. *Neurosci Lett* 2006;404:222–226.
- 17 Camiña JP, Campos JF, Caminos JE, et al: Obestatin-mediated proliferation of human retinal pigment epithelial cells: regulatory mechanisms. *J Cell Physiol* 2007;211:1–9.
- 18 Mészárosóvá M, Sirotkin AV, Grossmann R, et al: The effect of obestatin on porcine ovarian granulosa cells. *Anim Reprod Sci* 2008;108:196–207.
- 19 Pazos Y, Alvarez CJ, Camiña JP, et al: Stimulation of extracellular signal-regulated kinases and proliferation in the human gastric cancer cells KATO-III by obestatin. *Growth Factors* 2007;25:373–381.
- 20 Kapica M, Zabielska M, Puzio I, et al: Obestatin stimulates the secretion of pancreatic juice enzymes through a vagal pathway in anaesthetized rats – preliminary results. *J Physiol Pharmacol* 2007;58:123–130.
- 21 Ren AJ, Guo ZF, Wang YK, et al: Inhibitory effect of obestatin on glucose-induced insulin secretion in rats. *Biochim Biophys Res Commun* 2008;369:969–972.
- 22 Banks WA, Tschoep M, Robinson SM, et al: Extent and direction of ghrelin transport across the blood-brain barrier is determined by its unique primary structure. *J Pharmacol Exp Ther* 2002;302:822–827.
- 23 Pan W, Tu H, Kastin AJ: Differential BBB interactions of three ingestive peptides: obestatin, ghrelin, and adiponectin. *Peptides* 2006;27:911–916.
- 24 Bresciani E, Rapetti D, Donà F, et al: Obestatin inhibits feeding but does not modulate GH and corticosterone secretion in the rat. *J Endocrinol Invest* 2006;29:16–18.
- 25 Yamamoto D, Ikeshita N, Daito R, et al: Neither intravenous nor intracerebroventricular administration of obestatin affects the secretion of GH, PRL TSH and ACTH in rats. *Regul Pept* 2007;138:141–144.
- 26 Samson WK, White MM, Price C, et al: Obestatin acts in brain to inhibit thirst. *Am J Physiol Regul Integr Comp Physiol* 2007;292:637–643.
- 27 Samson WK, Yosten G, Chang JK, et al: Obestatin inhibits vasopressin secretion: evidence for a physiological action in the control of fluid homeostasis. *J Endocrinol* 2008;196:559–564.
- 28 Nogueiras R, Pfluger P, Tovar S, et al: Effects of obestatin on energy balance and growth hormone secretion in rodents. *Endocrinology* 2007;148:21–26.
- 29 Gourcerol G, Tache Y: Obestatin – a ghrelin-associated peptide that does not hold its promise to suppress food intake and motility. *Neurogastroenterol Motil* 2007;19:161–165.
- 30 Huda MS, Durham BH, Wong SP, et al: Plasma obestatin levels are lower in obese and post-gastrectomy subjects, but do not change in response to a meal. *Int J Obes* 2008;32:129–135.
- 31 Zamrazilová H, Hainer V, Sedláčková D, et al: Plasma obestatin levels in normal weight, obese and anorectic women. *Physiol Res* 2008;57:49–55.
- 32 Nakahara T, Harada T, Yasuhara D, et al: Plasma obestatin concentrations are negatively correlated with body mass index, insulin resistance index, and plasma leptin concentrations in obesity and anorexia nervosa. *Biol Psychiatry* 2008;64:252–255.
- 33 Mafra D, Guebre-Egziabher F, Cleaud C, et al: Obestatin and ghrelin interplay in hemodialysis patients. *Nutrition* 2010;26:1100–1104.
- 34 Lacquaniti A, Bolognani D, Donato V, et al: Obestatin: a new element for mineral metabolism and inflammation in patients on hemodialysis. *Kidney Blood Press Res* 2011;34:104–110.
- 35 Lacquaniti A, Donato V, Chirico V, et al: From chronic kidney disease to transplantation: the roles of obestatin. *Regul Pept* 2011;171:48–52.
- 36 Zou CC, Liang L, Wang CL, Fu JF, Zhao ZY: The change in ghrelin and obestatin levels in obese children after weight reduction. *Acta Paediatr* 2009;98:159–165.
- 37 Butler MG, Bittel DC: Plasma obestatin and ghrelin levels in subjects with Prader-Willi syndrome. *Am J Med Genet* 2007;143:413–414.
- 38 Qader SS, Håkanson R, Rehfeld JF, et al: Proghrelin-derived peptides influence the secretion of insulin, glucagon, pancreatic polypeptide and somatostatin: a study on isolated islets from mouse and rat pancreas. *Regul Pept* 2008;146:230–237.
- 39 Egido EM, Hernández R, Marco J, Silvestre RA: Effect of obestatin on insulin, glucagon and somatostatin secretion in the perfused rat pancreas. *Regul Pept* 2009;152:61–66.
- 40 Fontenot E, DeVente JE, Seidel ER: Obestatin and ghrelin in obese and in pregnant women. *Peptides* 2007;28:1937–1944.
- 41 Kellokoski E, Kunnari A, Jokela M, et al: Ghrelin and obestatin modulate early atherogenic processes on cells: enhancement of monocyte adhesion and oxidized low-density lipoprotein binding. *Metab Clin Exp* 2009;58:1572–1580.
- 42 Ozbay Y, Aydin S, Dagli AF, et al: Obestatin is present in saliva: alterations in obestatin and ghrelin levels of saliva and serum in ischemic heart disease. *BMB Reports* 2008;41:55–61.
- 43 Ren AJ, He Q, Shi JS, et al: Association of obestatin with blood pressure in the third trimesters of pregnancy. *Peptides* 2009;30:1742–1745.
- 44 Alvarez CJ, Lodeiro M, Theodoropoulou M, et al: Obestatin stimulates Akt signaling in gastric cancer cells through beta-arrestin-mediated epidermal growth factor receptor transactivation. *Endocr Relat Cancer* 2009;16:599–611.
- 45 Volante M, Rosas R, Ceppi P, et al: Obestatin in human neuroendocrine tissues and tumours: expression and effect on tumour growth. *J Pathol* 2009;218:458–466.
- 46 Iglesias MJ, Salgado A, Piñeiro R, et al: Lack of effect of the ghrelin gene-derived peptide obestatin on cardiomyocyte viability and metabolism. *J Endocrinol Invest* 2007;30:470–476.
- 47 Zhang Z, Zou D, Chen Y, et al: Obestatin inhibits proliferation and differentiation of 3T3-L1 preadipocytes. *Acad J Sec Mil Med Univ* 2007;28:929–932.
- 48 Alnema MM, Aydin S, Ozkan Y, et al: Ghrelin and obestatin expression in oral squamous cell carcinoma: an immunohistochemical and biochemical study. *Mol Cell Biochem* 2010;339:173–179.
- 49 Chen C, Asakawa A, Fujimiya M, Lee S, Inui A: Ghrelin gene products and the regulation of food intake and gut motility. *Pharmacol Rev* 2009;61:430–481.
- 50 Perboni S, Inui A: Appetite and gastrointestinal motility: role of ghrelin-family peptides. *Clin Nutr* 2010;29:227–234.