

GHRELIN: AN OREXIGENIC SIGNAL

Kaur Inderjeet¹, Badyal Ashima^{2*}, Sodhi K S³, Pandey R⁴.

¹Postgraduate Student (MD), Department of Medicine, SGRD, Amritsar, India.

²Demonstrator, Department of Biochemistry, Government Medical College, Jammu, J&K State, India- 180001

³Professor, Department of Biochemistry, MMIMSR, Mullana, Ambala, Haryana.

⁴Professor and Head, Department of Biochemistry, MMIMSR, Mullana, Ambala, Haryana.

***Correspondence for Author: Badyal Ashima**

Demonstrator, Department of Biochemistry, Government Medical College, Jammu, J&K State, India- 180001

Article Received on 07/09/2015

Article Revised on 29/10/2015

Article Accepted on 20/11/2015

ABSTRACT

Recent progress in the field of energy homeostasis has been triggered by the discovery of a novel gastric hormone ghrelin, which is an endogenous agonist at the growth hormone secretagogue receptor and belongs to the motilin-related family of regulatory peptides. In addition to its ability to stimulate GH secretion and gastric motility, ghrelin stimulates appetite (orexigenic effect) and induces a positive energy balance leading to body weight gain. Ghrelin is a novel neuroendocrine signal possessing a wide spectrum of biological activities thereby illustrating the importance of the stomach in providing input into the brain. Defective ghrelin signaling from the stomach could contribute to abnormalities in energy balance, growth, and associated gastrointestinal and neuroendocrine functions. Here, we review the evidence indicating ghrelin as a crucial missing link between the stomach and the hypothalamus, and the clinical implication of this ghrelin signalling pathway in the control of gastrointestinal function, energy balance and growth.

KEYWORDS: Ghrelin, appetite, orexigenic, brain, stomach.

INTRODUCTION

Ghrelin, which acts as “meal initiation” or the “hunger hormone”, also known as lenomorelin, is a peptide hormone produced by ghrelinergic cells in the gastrointestinal tract^[1] which functions as a neuropeptide in the central nervous system.^[2] Besides regulating appetite, ghrelin also plays a significant role in regulating the stimulation of gut motility and gastric acid secretion, modulation of sleep, taste sensation and reward seeking behaviour, regulation of glucose metabolism, suppression of brown fat thermogenesis, modulation of stress and anxiety, protection against muscle atrophy, improvement of cardiovascular functions such as vasodilatation and cardiac contractility. When the stomach is empty, ghrelin is secreted. When the stomach is stretched, secretion stops.^[3] It acts on hypothalamic cells both to increase hunger, and to increase gastric acid secretion and gastrointestinal motility to prepare the body for food intake^[4].

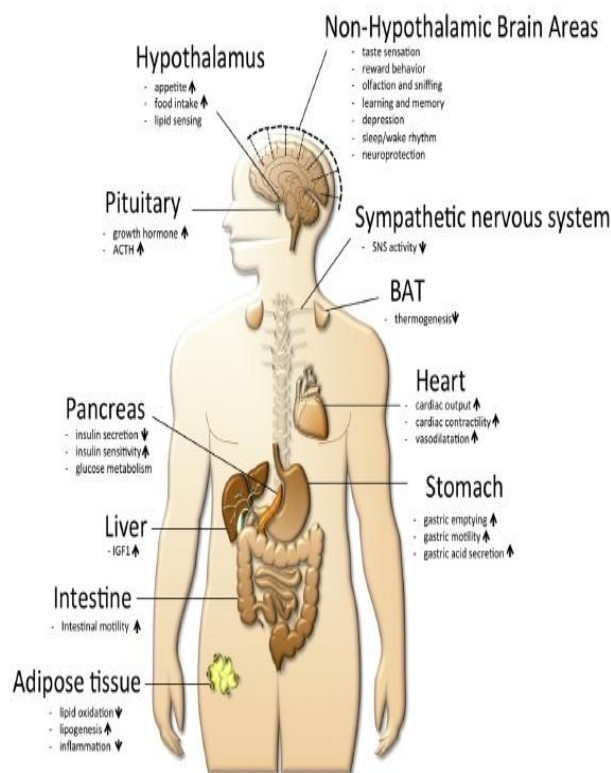


Figure 1: Schematic on ghrelin’s physiological effects.

HISTORY

Kojima and Kangawa identified the 28 amino acid peptide ghrelin as an endogenous ligand for the “orphan” GHS (Ghrelin/Growth Hormone Secretagogue Receptor).^[5] Ghrelin was discovered after the ghrelin receptor (called growth hormone secretagogue type 1A receptor or GHSR) was discovered in 1996^[6] and was reported in 1999.^[7] The hormone name is based on its role as a growth hormone-releasing peptide, with reference to the Proto-Indo-European root GHRE, meaning to grow (**G**rowth **H**ormone **R**elease-**I**nducing = Ghrelin).^[8]

SYNTHESIS

The GHRL gene produces mRNA which has four exons. Five products arise: the first is the 117-amino acid proghrelin (it is homologous to promotilin; both are members of the motilin family). It is cleaved to produce proghrelin which is further cleaved to produce a 28-amino acid ghrelin (unacylated) and C-ghrelin (acylated). Obestatin is presumed to be cleaved from C-ghrelin.^[9]

Ghrelin only becomes active when caprylic (octanoic) acid is linked post-translationally to serine at the 3-position by the enzyme ghrelin O-acyltransferase (GOAT). It is located on the cell membrane of ghrelin cells in the stomach and pancreas.^[10] The non-octanoylated form is desacyl ghrelin. It does not activate the GHSR receptor but does have other effects: cardiac,^[11] anti-ghrelin,^[12] appetite stimulation,^[13] and inhibition of hepatic glucose output.^[14] Side-chains other than octanoyl have also been observed: these can also trigger the ghrelin receptor.^[15] In particular, decanoyl ghrelin has been found to constitute a significant portion of circulating ghrelin in mice, but as of 2011 its presence in humans has not been established.^[16]

GHRELIN AND THE GUT-BRAIN AXIS

Ghrelin has been recognized as an important regulator of GH secretion and energy balance. Orexigenic and adipogenic ghrelin is produced by and released from the

stomach in response to fasting and hypoglycemia. Ghrelin and leptin regulate gastric motility, appetite, and body weight by counter-regulating the same hypothalamic signals such as neuropeptide Y (NPY) and agouti-related peptide (AGRP), the two extraordinarily potent orexigenic peptides that simultaneously decrease energy expenditure. NPY and AGRP are coproduced in the arcuate nucleus (ARC) and act in the paraventricular nucleus (PVN) and adjacent hypothalamic areas such as the lateral hypothalamic area (LHA) in which orexin neurons exist. Ghrelin is a novel neuroendocrine peptide that links the gastrointestinal system and the hypothalamic orexigenic pathway. Ghrelin is expressed mainly in the stomach, by neuroendocrine cells (X/A-like cells in rodents and P/D1 cells in humans) in the fundus, and is secreted into the circulation.^[17]

MECHANISM OF ACTION

Ghrelin is a participant in regulating the complex process of energy homeostasis which adjusts both energy input - by adjusting hunger signals - and energy output - by adjusting the proportion of energy going to ATP production, fat storage, glycogen storage, and short-term heat loss. The net result of these processes is reflected in body weight, and is under continuous monitoring and adjustment based on metabolic signals and needs. At any given moment, it may be in equilibrium or disequilibrium. Gastric-brain communication is an essential part of energy homeostasis, and several communication pathways are probable, including the gastric intracellular mTOR/S6K1 pathway mediating the interaction among ghrelin, nesfatin and endocannabinoid gastric systems, and both afferent and efferent vagal signals. Ghrelin and synthetic ghrelin mimetics (growth hormone secretagogues) increase appetite and fat mass by triggering receptors in the arcuate nucleus that include the orexigenic NPY neurons.^[18-20] Furthermore, Ghrelin mimetics have been investigated as diagnostic agents to establish growth hormone deficiency as well as a therapeutic option for age dependent growth hormone decline and have yielded some potentially beneficial effects (Table 1).

Table 1: Summary of ghrelin mimetics tested in clinical trials.

Compound	Active/Inactive	Indication
Ghrelin mimetic		
Pralmorelin	Approved	Diagnostic for GH deficiency
Macimorelin	Phase III	Diagnostic for GH deficiency
Anamorelin	Phase III	Anorexia/Cancer cachexia
Relamorelin	Phase IIb	Diabetic gastroparesis
Ulimorelin	Inactive	Opioid induced constipation/GI functions
Ipamorelin	Inactive	GI functional disorders
Carpromorelin	Inactive	Frailty in elderly
CP 464709	Inactive	Frailty in elderly
Tabimorelin	Inactive	GH deficiency
Ibutamorelin	Inactive	Frailty in elderly
Examorelin/Hexarelin	Inactive	GH release
SM 130686	Inactive	Growth hormone deficiency
LY 426410/LY 444711	Inactive	GH release

FUNCTIONS

Ghrelin-responsiveness of target neurons is both leptin- and insulin-sensitive.^[21] Ghrelin reduces the mechanosensitivity of gastric vagal afferents, so they are less sensitive to gastric distension. In addition to its function in energy homeostasis, ghrelin also activates the mesolimbic cholinergic-dopaminergic reward link, a circuit that communicates the hedonic and reinforcing aspects of natural rewards, such as food and addictive drugs such as ethanol. Ghrelin receptors are located on neurons in this circuit and hypothalamic ghrelin signalling is required for reward from alcohol and palatable/rewarding foods.^[22] Ghrelin also improves endothelial function and inhibits proatherogenic changes in cell cultures. It activates the endothelial isoform of nitric oxide synthase in a pathway that depends on various kinases. Ghrelin has been linked to inducing appetite and feeding behaviours. Circulating ghrelin levels are the highest right before a meal and the lowest right after. Body weight is regulated through energy balance, the amount of energy taken in versus the amount of energy expended over an extended period of time. Studies have shown that ghrelin levels are negatively correlated with weight. This data suggests that ghrelin functions as an adiposity signal, a messenger between the body's energy stores and the brain. When a person loses weight, ghrelin levels increase, which causes increased food consumption and weight gain. On the other hand, when a person gains weight, ghrelin levels drop, leading to a decrease in food consumption and weight loss. This suggests that ghrelin acts as a body weight regulator, continuously keeping one's body weight and energy stores in check.^[23]

Ghrelin may have beneficial hemodynamic effects in humans via reducing cardiac afterload and increasing cardiac output without increasing heart rate. Ghrelin may cause inhibition of growth in breast cancer,^[24] thyroid cancer,^[25] and lung cancer^[26] cell lines, which are independent of the GH-releasing effect. In contrast, ghrelin may induce a proliferative response in cell lines of hepatoma and those of prostate cancer in which IGF-1 and GH may have tumorigenic potential. Since both ghrelin and des-acyl ghrelin inhibit cell death in cardiomyocytes and endothelial cells, acylation of the peptide is needed for endocrine actions. These findings indicate the existence of additional receptor subtypes that may exhibit different affinities for ghrelin/GHS and different pathophysiological relevance.^[27]

Ghrelin expression is reported in gastrointestinal and pancreatic endocrine tumors and gastric neuroendocrine cell hyperplasia. Ghrelin-producing endocrine tumors may help in better understanding ghrelin functions in humans and screening of circulating ghrelin levels for diagnostic work-up. Ghrelin may also directly stimulate the differentiation of pre-adipocytes and inhibit lipolysis, suggesting a role in the process of adipogenesis. Ghrelin may increase anxiety-like behavior and memory retention and may be a sleep-promoting factor. Since the

GHS receptors are widely distributed, many other physiological effects of ghrelin may remain to be uncovered.^[28]

GHRELIN SECRETION IN RESPONSE TO EXTERNAL FOOD CUES

External food cues such as sight, smell, and taste trigger the cephalic phase of ingestive behaviour, which consists of it increased gut motility, gut hormone secretion, and autonomic arousal. This response in turn triggers central arousal and incentive mechanisms that promote food consumption. The cephalic response include ghrelin release, which increases after exposure to food cues in humans. Conversely, recent evidence suggests that anticipation of the caloric content of an investigator-supplied milkshake modulates the postprandial reduction in ghrelin levels. When subjects believed they were consuming a high calorie rather than 'a healthy' milkshake, their ghrelin levels were much more reduced. In sum, ghrelin secretion is a part CNS to activate hypothalamic and dopaminergic feeding centers. This feedback allows other factors such as chronic stress, negative energy balance, leptin and insulin to affect motivation to feed by enhancing or reducing the cephalic release of ghrelin.^[29]

CLINICAL SIGNIFICANCE

Ghrelin has inhibitory effects on gonadotropin-releasing hormone (GnRH) secretion. It may cause decreased fertility. Ghrelin is produced early by the fetal lung and promotes lung growth. Cord blood levels of active and total ghrelin show a correlation between ghrelin levels and birth weight. Ghrelin gene products have several actions on acute and chronic inflammation and autoimmunity, with promising therapeutic applications. Ghrelin levels in the plasma of obese individuals are lower than those in leaner individuals, suggesting that ghrelin does not contribute to obesity, except in the cases of Prader-Willi syndrome-induced obesity, characterized by severe hyperphagia, GH deficiency, hypogonadism, neonatal hypotonia, dysmorphic features and cognitive impairment. Although Prader-Willi syndrome arises from functional loss of several paternally expressed genes in an imprinted domain on chromosome 15, mediators of the phenotype are not well known. Recent studies demonstrated that while obesity per se is associated with low ghrelin levels, that accompanied by Prader-Willi syndrome is associated with elevated ghrelin with no decrease after a meal. The increased ghrelin levels are comparable to or higher than those reported to stimulate appetite and food intake during exogenous ghrelin administration in humans,^[30] suggesting a role of ghrelin in the pathogenesis of hyperphagia in Prader-Willi syndrome where high ghrelin levels are correlated with increased food intake. Those with anorexia nervosa have high plasma levels of ghrelin compared to both the constitutionally thin and normal-weight controls.

The level of ghrelin increases during the time of day from midnight to dawn in thinner people, which suggests there is a flaw in the circadian rhythm of obese individuals. Ghrelin levels reflect release in a circadian rhythm which can be interrupted by exposure to light at night. Short sleep duration may also lead to obesity, through an increase of appetite via hormonal changes. Lack of sleep increases ghrelin, and decreases leptin, both effects producing increased hunger and obesity. Ghrelin levels are high in patients with cancer-induced cachexia.^[31] Gastric bypass surgery not only reduces the gut's capacity for food but also dramatically lowers ghrelin levels compared to both lean controls and those that lost weight through dieting alone. However, studies are conflicting as to whether or not ghrelin levels return to nearly normal with gastric bypass patients in the long term after weight loss has stabilized. Bariatric surgeries involving vertical sleeve gastrectomy reduce plasma ghrelin levels by about 60% in the long term. In rodents and pigs, an anti-obesity vaccine has been developed: it blocks the ghrelin receptor. Ghrelin plasma concentration increases with age and this may contribute to the tendency for weight gain as people age.^[32]

CONCLUSIONS AND FUTURE PERSPECTIVES

Ghrelin has illustrated the importance of functional interdependency of the stomach and hypothalamus, providing a crucial missing link in the regulation of energy balance, growth, and the coordinated gastrointestinal function. Ghrelin may be a counterpart to leptin and a key afferent component in this system. Characterization of the gene encoding ghrelin and its overall genomic structure has enabled genomic screening of the ghrelin gene. Recent studies suggest that Arg51Gln or Leu72Met polymorphism of proghrelin gene may be associated with lower plasma ghrelin and insulin resistance or lower fat accumulation. However, Leu72Met polymorphism may be associated with obesity in children and may modulate glucose-induced insulin secretion. The finding that plasma ghrelin concentrations at baseline are more alike within pairs of twins than between pairs indicates a probable genetic effect underlying the variability in plasma ghrelin levels. Further studies are warranted to examine whether genetic variation at ghrelin or its receptor locus could be a genetic factor determining fat accumulation and statural growth. In the next few years, we foresee a rapid increase of knowledge in such basic mechanisms in healthy and diseased subjects, as well as in the diagnostic and therapeutic uses of natural (ghrelin) and artificial GHSs. It will become apparent whether ghrelin is the sole ligand or one of a number of ligands activating the GHS receptor and whether GHS-R1a is the sole receptor or one of a group of receptors for such ligands. Synthetic ghrelin administration for cachexia, hemodialysis, seizure control and gastroparesis are being investigated.

REFERENCES

- Inui A, Asakawa A, Bowers CY, Mantovani G, Laviano A, Meguid MM, Fujimiya M. "Ghrelin,

- appetite, and gastric motility: the emerging role of the stomach as an endocrine organ". *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, 2004; 18(3): 439–56.
- Dickson SL, Egecioglu E, Landgren S, Skibicka KP, Engel JA, Jerlhag E. "The role of the central ghrelin system in reward from food and chemical drugs". *Molecular and Cellular Endocrinology*, 2011; 340(1): 80–87.
- Burger KS, Berner LA. "A functional neuroimaging review of obesity, appetitive hormones and ingestive behavior". *Physiology & Behavior*, 2014; 136: 121–7.
- Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. "Central nervous system control of food intake". *Nature*, 2000; 404(6778): 661–71.
- Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., Kangawa, K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature (London)*, 1999; 402: 656-660.
- Howard AD, Feighner SD, Cully DF, Arena JP, Liberatore PA, et al. "A receptor in pituitary and hypothalamus that functions in growth hormone release". *Science (New York, N.Y.)*, 1996; 273(5277): 974–7.
- Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. "Ghrelin is a growth-hormone-releasing acylated peptide from stomach". *Nature*, 1999; 402(6762): 656–60.
- Inui A, Asakawa A, Bowers CY, Mantovani G, Laviano A, Meguid MM, Fujimiya M. "Ghrelin, appetite, and gastric motility: the emerging role of the stomach as an endocrine organ". *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, 2004; 18(3): 439–56.
- Seim I, Amorim L, Walpole C, Carter S, Chopin LK, Herington AC. "Ghrelin gene-related peptides: multifunctional endocrine / autocrine modulators in health and disease". *Clinical and Experimental Pharmacology & Physiology*, 2010; 37(1): 125–31.
- Castañeda TR, Tong J, Datta R, Culler M, Tschop MH. "Ghrelin in the regulation of body weight and metabolism". *Frontiers in Neuroendocrinology*, 2010; 31(1): 44–60.
- Bedendi I, Alloati G, Marcantoni A, Malan D, Catapano F, Ghé C, Deghenghi R, Ghigo E, Muccioli G. "Cardiac effects of ghrelin and its endogenous derivatives des-octanoyl ghrelin and des-Gln14-ghrelin". *European Journal of Pharmacology*, 2003; 476(1,2): 87–95.
- Broglio F, Gottero C, Prodham F, Gauna C, Muccioli G, Papotti M, Abribat T, Van Der Lely AJ, Ghigo E. "Non-acylated ghrelin counteracts the metabolic but not the neuroendocrine response to acylated ghrelin in humans". *The Journal of Clinical Endocrinology and Metabolism*, 2004; 89(6): 3062–5.
- Toshinai K, Yamaguchi H, Sun Y, Smith RG, Yamanaka A, Sakurai T, Date Y, Mondal MS,

- Shimbara T, Kawagoe T, Murakami N, Miyazato M, Kangawa K, Nakazato M. "Des-acyl ghrelin induces food intake by a mechanism independent of the growth hormone secretagogue receptor". *Endocrinology*, 2006; 147(5): 2306–14.
14. Gauna C, Delhanty PJ, Hofland LJ, Janssen JA, Broglio F, Ross RJ, Ghigo E, van der Lely AJ. "Ghrelin stimulates, whereas des-octanoyl ghrelin inhibits, glucose output by primary hepatocytes". *The Journal of Clinical Endocrinology and Metabolism*, 2005; 90(2): 1055–6.
 15. Korbonits M, Goldstone AP, Gueorguiev M, Grossman AB. "Ghrelin--a hormone with multiple functions". *Frontiers in Neuroendocrinology*, 2004; 25(1): 27–68.
 16. Stengel A, Taché Y. "Interaction between gastric and upper small intestinal hormones in the regulation of hunger and satiety: ghrelin and cholecystokinin take the centre stage". *Current Protein & Peptide Science*, 2011; 12(4): 293–304.
 17. Kojima, M., Hosoda, H., Sawaguchi, A., Mondal, M. S., Suganuma, T., Matsukura, S., Kangawa, K., Nakazato, M. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology*, 2000; 141: 4255-4261.
 18. Hewson AK, Dickson SL. "Systemic administration of ghrelin induces Fos and Egr-1 proteins in the hypothalamic arcuate nucleus of fasted and fed rats". *Journal of Neuroendocrinology*, 2000; 12(11): 1047–1049.
 19. Dickson SL, Leng G, Robinson IC. "Systemic administration of growth hormone-releasing peptide activates hypothalamic arcuate neurons". *Neuroscience*, 1993; 53(2): 303–306.
 20. Dickson SL, Luckman SM. "Induction of c-fos messenger ribonucleic acid in neuropeptide Y and growth hormone (GH)-releasing factor neurons in the rat arcuate nucleus following systemic injection of the GH secretagogue, GH-releasing peptide-6". *Endocrinology*, 1997; 138(2): 771–777.
 21. Hewson AK, Tung LY, Connell DW, Tookman L, Dickson SL. "The rat arcuate nucleus integrates peripheral signals provided by leptin, insulin, and a ghrelin mimetic". *Diabetes*, 2002; 51(12): 3412–3419.
 22. Page AJ, Slattery JA, Milte C, Laker R, O'Donnell T, Dorian C, Brierley SM, Blackshaw LA. "Ghrelin selectively reduces mechanosensitivity of upper gastrointestinal vagal afferents". *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 2007; 292(5): 1376–1384.
 23. Skibicka KP, Hansson C, Egecioglu E, Dickson SL. "Role of ghrelin in food reward: impact of ghrelin on sucrose self-administration and mesolimbic dopamine and acetylcholine receptor gene expression". *Addiction Biology*, 2012; 17(1): 95–107.
 24. Cassoni, P., Papotti, M., Catapano, F., Ghe, C., Deghenghi, R., Ghigo, E., Muccioli, G. Specific binding sites for synthetic growth hormone secretagogues in non-tumoral and neoplastic human thyroid tissue. *J. Endocrinol.* 2000; 165: 139-146.
 25. Ghe, C., Cassoni, P., Catapano, F., Marrocco, T., Deghenghi, R., Ghigo, E., Muccioli, G., Papotti, M. The antiproliferative effect of synthetic peptidyl GH secretagogues in human CALU-1 lung carcinoma cells. *Endocrinology*, 2002; 143: 484-49.
 26. Papotti, M., Cassoni, P., Volante, M., Deghenghi, R., Muccioli, G., Ghigo, E. Ghrelin-producing endocrine tumors of the stomach and intestine. *J. Clin. Endocrinol. Metab.* 2001; 86: 5052-5059.
 27. Asakawa, A., Inui, A., Kaga, T., Yuzuriha, H., Nagata, T., Fujimiya, M., Katsuura, G., Makino, S., Fujino, M. A., Kasuga, M. A role of ghrelin in neuroendocrine and behavioral responses to stress in mice. *Neuroendocrinology*, 2001; 74: 143-147.
 28. Weikel, J. C., Wichniak, A., Ising, M., Brunner, H., Friess, E., Held, K., Mathias, S., Schmid, D. A., Uhr, M., Steiger, A. Ghrelin promotes slow-wave sleep in humans. *Am. J. Physiol.* 2003; 284: 407-415.
 29. Crum A, Corbin W R, Brownwell K D, Salovey P. Mind over milkshakes: mindsets not just nutrients, determine ghrelin response. *Health PSYCHOLOGY: official Journal of the division of health psychology, American psychological association*, 2011; 30: 424-429.
 30. Wren, A. M., Seal, L. J., Cohen, M. A., Brynes, A. E., Frost, G. S., Murphy, K. G., Dhillon, W. S., Ghatei, M. A., Bloom, S. R. Ghrelin enhances appetite and increases food intake in humans. *J. Clin. Endocrinol. Metab.*, 2001; 86: 5992-5995
 31. Garcia JM, Garcia-Touza M, Hijazi RA, Taffet G, Epner D, Mann D, Smith RG, Cunningham GR, Marcelli M. "Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia". *The Journal of Clinical Endocrinology and Metabolism*, 2005; 90(5): 2920–6.
 32. Vizcarra JA, Kirby JD, Kim SK, Galyean ML. "Active immunization against ghrelin decreases weight gain and alters plasma concentrations of growth hormone in growing pigs". *Domestic Animal Endocrinology*, 2007, 33(2): 176–8.