BioVendor R&D®

Ghrelin and Obestatin

Twin proteins encoded by the one gene

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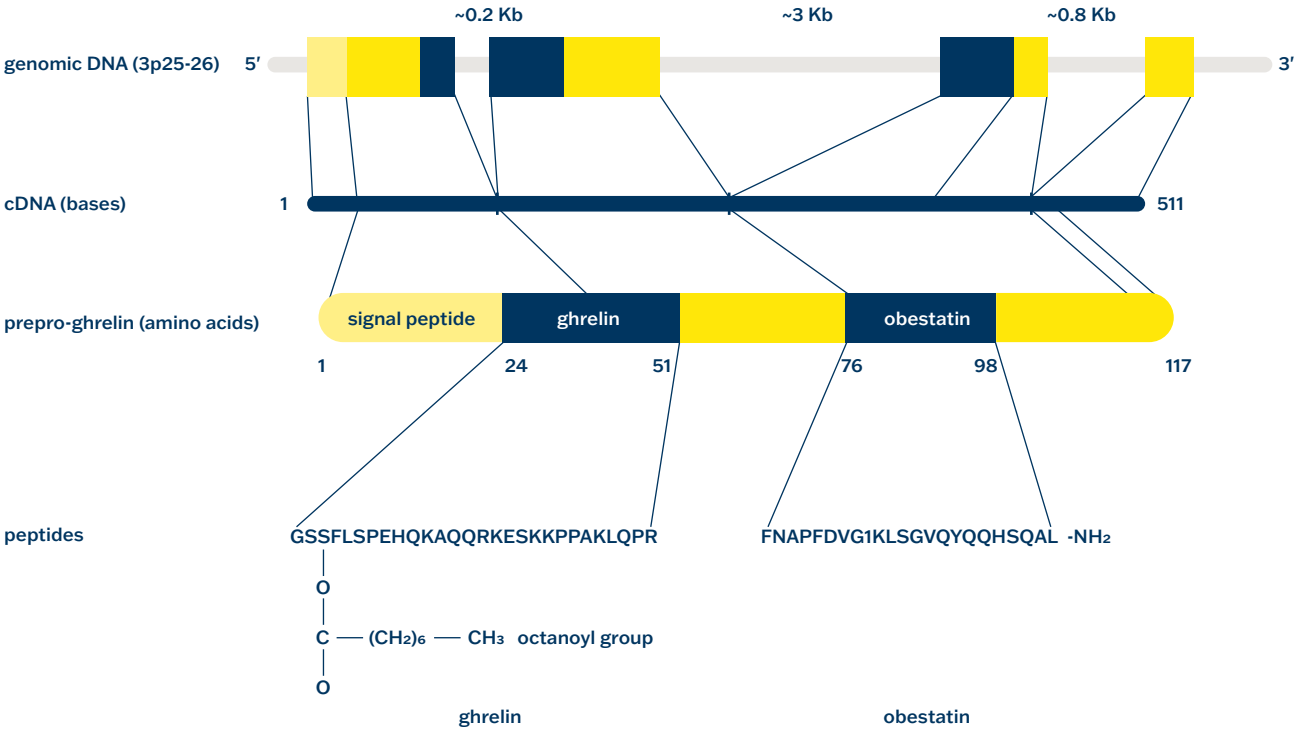
Introduction

Human ghrelin gene and its peptide products



The gene GHRL encodes the ghrelin-obestatin preproprotein that is cleaved to yield two peptides, ghrelin and obestatin.

Ghrelin is a powerful appetite stimulant and plays an important role in energy homeostasis. Its secretion is initiated when the stomach is empty, whereupon it binds to the growth hormone secretagogue receptor in the hypothalamus which results in the secretion of growth hormone. Ghrelin is thought to regulate multiple activities, including hunger, reward perception via the mesolimbic pathway, gastric acid secretion, gastrointestinal motility, and pancreatic glucose-stimulated insulin secretion.

It was initially proposed that **obestatin** plays an opposing role to ghrelin by promoting satiety and thus decreasing food intake, but this action is still debated. Recent reports suggest multiple metabolic roles for obestatin, including regulating adipocyte function and glucose metabolism.

Discover uniques assays for measurement of ghrelins and obestatin in energy metabolism

- most reliable measurements in various sample types
- control in data reproducibility, tracebility and consistence
- tools for clinical and preclinical trials

Ghrelin

Ghrelin has been discovered in 1999 and Kojima & Kangawa showed ghrelin as the first peptidic hormone to become activated by acylation. However, the initially established assays for determination of ghrelin circulating in biological samples (blood/plasma) were quite rapidly set-up but often without caring about the reliability of Acylated Ghrelin values and mixing content of both forms (Acylated and Unacylated Ghrelin) and sample collection remained a major challenge. Currently, while Acylated Ghrelin is known as the active form of the peptide, and as the only form for which a receptor has been identified, clinical trials have shown positive results using the Unacylated form. The underlying mechanisms are not yet well understood, and several teams in the world are currently working on this topic.

Clinical challenges

Ghrelin is now a well-known orexigenic hormone leading to an increase in appetite. It has become an obvious target for treatment of eating disorders like obezity or anorexia nervosa. However, we know that Ghrelin is also implicated in many other physiological systems like the cardiovascular, bone, gastrointestinal and immune systems as well as some physio-pathological states like mood or muscle mass maintenance, heart failure, myocardial infarction, cachexia, cancer or Prader-Willi syndrome. Since bioanalysis tools such as the BioVendor Ghrelin ELISA assay kits are now available, it will become progressively easier to elucidate the role of this new hormone as well as its therapeutic implications.

Initially launched assays were often without caring about the reliability of Acylated Ghrelin values and mixing content of both forms (Acylated and Unacylated Ghrelin). First results were either nonspecific (measuring Acylated and Unacylated forms) or leading to falsely low values due to Ghrelin deacylation/degradation as the consequence. Despite those biased results, the existence of a Ghrelin pulse has been established, and has been characterized to manifest as a peak before meal times, followed by a rapid decrease postprandial. However, a number of inconsistencies remain between the different results obtained in clinical studies due to a lack of reliable tools to measure Acylated Ghrelin.

Clinical relevance
- growth hormon research
- a gut peptidic hormone with an important role in **stimulation of appetite, food intake and glucose homeostasis**, therefore relevant tool in the research of diabetes, obezity, anorexia, cancer cachexia or gastroparesis
- alcohol addiction
- COPD

Reference
Strasser F. Clinical application of ghrelin. Curr Pharm Des. 2012;18(31):4800-12
Schalla M.A., Stengel A. The Role of Ghrelin in Anorexia Nervosa. Int. J. Mol. Sci. 2018;19:2117

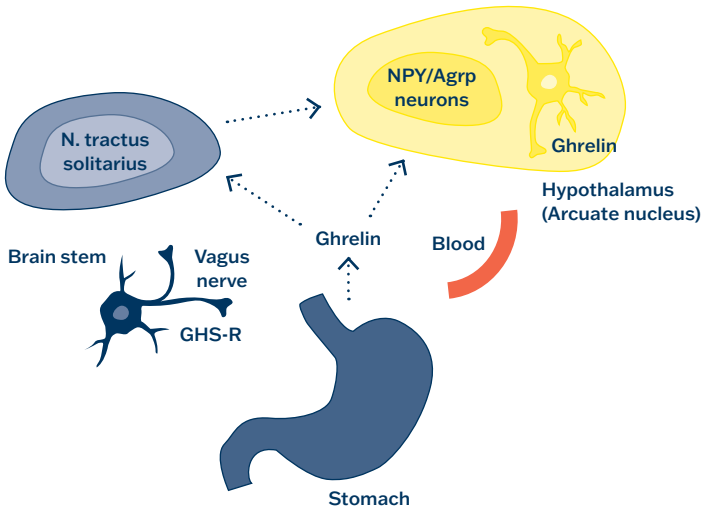
Fujimiya M., Ataka K., Asakawa A., Chen C.Y., Kato I., Inui A. Regulation of gastroduodenal motility: Acyl ghrelin, des-acyl ghrelin and obestatin and hypothalamic peptides. Digestion. 2012;85:90–94

Tuero C, Valenti V, Rotellar F, Landecho MF, Cienfuegos JA, Frühbeck G. Revisiting the Ghrelin Changes Following Bariatric and Metabolic Surgery. Obes Surg. 2020 Jul;30(7):2763-2780

Farokhnia M, Grodin EN, Lee MR, Oot EN, Blackburn AN, Stangl BL, Schwandt ML, Farinelli LA, Momenan R, Ramchandani VA, Leggio L. Exogenous ghrelin administration increases alcohol self-administration and modulates brain functional activity in heavy-drinking alcohol-dependent individuals. Mol Psychiatry. 2018 Oct;23(10):2029-2038

Zhang X, Yang T, Wang J, Feng M, Hou Y, Shen Y, Chen L. Elevated circulating ghrelin in patients with COPD: A meta-analysis. Chron Respir Dis. 2018 Nov;15(4):365-373

A



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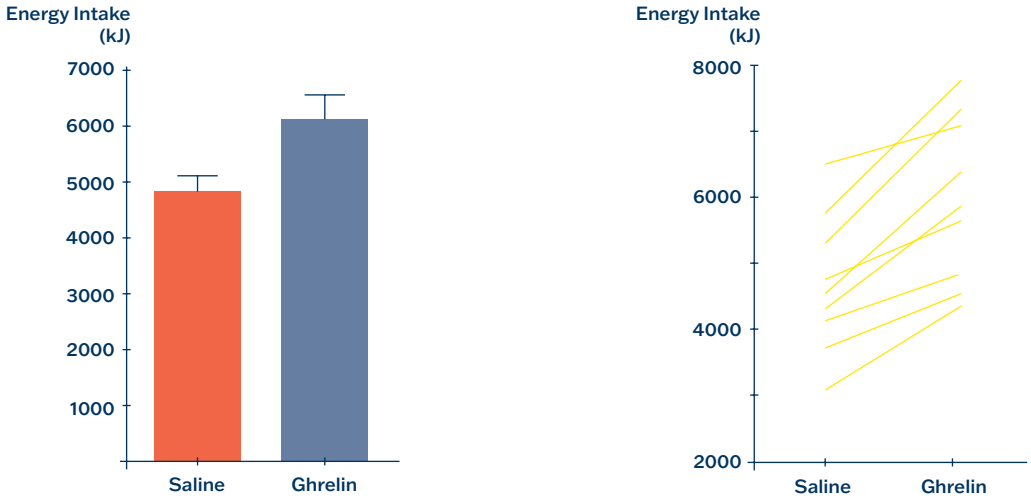

Figure:

A) Role of endogenous ghrelin in appetite regulation. B) The effect of ghrelin versus saline on appetite and food intake - mean energy intake from free choice buffet, and individual changes in energy intake from free choice buffet , *** $p < 0.001$

Reference
Wren A.M. et al. Ghrelin enhances appetite and increases food intake in humans, J. Clinical Endocrinology & Metabolism, 86:5992–5995 (2001)

Ordering information

Product	Cat.No.
Mouse/Rat Ghrelin Acylated Easy Sampling ELISA	RA394062500R
Mouse/Rat Ghrelin Acylated Express ELISA	RA394062400R
Mouse/Rat Ghrelin Unacylated Express ELISA	RA394063400R
Human Ghrelin Acylated Easy Sampling ELISA	RA194062500R
Human Ghrelin Unacylated Easy Sampling ELISA	RA194063500R
Human Ghrelin Acylated Express ELISA	RA194062400R
Human Ghrelin Unacylated Express ELISA	RA194063400R
Porcine Acylated Ghrelin ELISA	RA594062400R
Porcine Unacylated Ghrelin ELISA	RA594063400R

Obestatin

It was initially proposed that **obestatin** plays an opposing role to ghrelin by promoting satiety and thus decreasing food intake, but this action is still debated. Recent reports suggest multiple metabolic roles for obestatin, including regulating adipocyte function and glucose metabolism.

Clinical challenges

Obestatin was first reported to inhibit **jejunal contraction, food intake and body weight gain** in addition to antagonising ghrelin-induced contraction of isolated jejunum muscle. Obestatin reduced antral and duodenal motility in the fed state and to impede restoration of normal fasted-state duodenal activity. Potential actions on food intake and GI motility may occur, at least in part, via the vagal afferent pathway and central corticotrophin-releasing factor receptors.

Reference
Zhang JV., Ren PG. and Avsian-Kretchmer O. (2005): Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science.;310(5750):996-999.

Ataka K., Inui A., Asakawa A. et al., (2008): Obestatin inhibits motor activity in the antrum and duodenum in the fed state of conscious rats. Am J Physiol Gastrointest Liver Physiol ;294:G1210–G1218.

Obestatin causes **NO-dependent vasodilation** in the human circulation. This effect is preserved in obesity, where it is accompanied by reduced ET-1-mediated vasoconstriction. These latter observations make obestatin a promising target for vascular prevention in obesity and diabetes.

Reference
Cowan E, Burch KJ, Green BD, Grieve DJ. Obestatin as a key regulator of metabolism and cardiovascular function with emerging therapeutic potential for diabetes. Br J Pharmacol. 2016 Jul;173(14):2165-81

Schinzari F, Veneziani A, Mores N, Barini A, Di Daniele N, Cardillo C, Tesauro M. Vascular Effects of Obestatin in Lean and Obese Subjects. Diabetes. 2017 May;66(5):1214-1221

Obestatin protects against experimental **ulcerative colitis** via acute attenuation of lipid peroxidation and TH1-mediated inflammation, chronic suppression of polymorphonuclear leukocyte infiltration, induction of glutathione synthesis, improved mucosal blood flow and stimulation of cell proliferation in colonic mucosa, effects that may be mediated by activation of anti-inflammatory cytokines. Obestatin shows protective effects against ischaemia–reperfusion injury in rat ileum, while the ghrelin/obestatin ratio is reported to be elevated in patients with active inflammatory bowel diseases (Crohn's disease and colitis) compared with those in remission.

Reference
Pamukcu O, Kumral ZN, Ercan F, Yegen BÇ, Ertem D (2013). Anti-inflammatory effect of obestatin and ghrelin in dextran sulfate sodium–induced colitis in rats. J Pediatr Gastroenterol Nutr (2013) 57: 211–218

Matuszyk A, Ceranowicz P, Warzecha Z, Cieszkowski J, Bonior J, Jaworek J et al. (2015). Obestatin accelerates the healing of acetic acid-induced colitis in rats. Oxid Med Cell Longev 2016

Obestatin was reported to be secreted by human pancreatic islets and pancreatic beta cell lines, to enhance their viability in response to both starvation and cytokines and to inhibit apoptosis. Its **autocrine/paracrine role in pancreas** is coupled with its ability to modulate insulin levels and inflammation clearly supports further investigation of this peptide as a potential therapeutic target in diabetes

Reference
Pradhan G, Wu CS, Han Lee J, Kanikarla P, Guo S, Yechoor VK, Samson SL, Sun Y. Obestatin stimulates glucose-induced insulin secretion through ghrelin receptor GHS-R. Sci Rep. 2017 Apr 20;7(1):979

Cowan E, Burch KJ, Green BD, Grieve DJ. Obestatin as a key regulator of metabolism and cardiovascular function with emerging therapeutic potential for diabetes. Br J Pharmacol. 2016 Jul;173(14):2165-81

Granata R., Settanni F., Gallo D., Trovato L., Biancone L., Cantaluppi V., Nano R., Annunziata M., Campiglia P., Arnoletti E., 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

Ordering information

Product	Cat.No.
Human Obestatin ELISA	RA19025R
Mouse/Rat Obestatin ELISA	RA19014R

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