

Ghrelin receptor in GtoPdb v.2025.3

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Abstract

The ghrelin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee for the Ghrelin receptor [19]**) is activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (*GHRL*, *Q9UBU3*). A unique post-translational modification (octanoylation of Ser³, catalysed by ghrelin O-acyltransferase (*MBOAT4*, *Q96T53*) [138] is essential for binding and activation of ghrelin receptors in all tissues, including the hypothalamus and pituitary [61]. Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding [4], and receptor mutagenesis has indicated overlap of the ghrelin binding site with those for small molecule agonists and allosteric modulators of ghrelin function [47]. The authorities in Japan have in 2020 approved the orally active agonist anamorelin, for the treatment of anorexia in cancer patients [130]. *PF-05190457* is a small-molecule inverse agonist targeting the ghrelin receptor that has been progressed to phase I clinical trial for the treatment of alcoholism and has been demonstrated to decrease appetite [32]. An endogenous antagonist and inverse agonist called Liver enriched antimicrobial peptide 2 (Leap2), expressed primarily in hepatocytes and in enterocytes of the proximal intestine [38, 71] inhibits ghrelin receptor-induced GH secretion and food intake [38]. The secretion of Leap2 and ghrelin is inversely regulated under various metabolic conditions [74]. In cell systems the ghrelin receptor is constitutively active [48], and this property is responsible for modulation of D₂ receptor signalling [20], and is attenuated by a naturally occurring mutation (A204E) that is associated with familial short stature [96].

Contents

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References

1. Ariyasu H, Takaya K, Tagami T, Ogawa Y, Hosoda K, Akamizu T, Suda M, Koh T, Natsui K and Toyooka S *et al.*. (2001) Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. *J Clin Endocrinol Metab* **86**: 4753-8 [PMID:11600536]
2. Baldanzi G, Filigheddu N, Cutrupi S, Catapano F, Bonisconi S, Fubini A, Malan D, Baj G, Granata R and Broglio F *et al.*. (2002) Ghrelin and des-acyl ghrelin inhibit cell death in cardiomyocytes and endothelial cells through ERK1/2 and PI 3-kinase/AKT. *J Cell Biol* **159**: 1029-37 [PMID:12486113]
3. Bedendi I, Alloatti G, Marcantoni A, Malan D, Catapano F, Ghé C, Deghenghi R, Ghigo E and Muccioli G. (2003) Cardiac effects of ghrelin and its endogenous derivatives des-octanoyl ghrelin and des-Gln14-ghrelin. *Eur J Pharmacol* **476**: 87-95 [PMID:12969753]
4. Bednarek MA, Feighner SD, Pong SS, McKee KK, Hreniuk DL, Silva MV, Warren VA, Howard AD, Van Der Ploeg LH and Heck JV. (2000) Structure-function studies on the new growth hormone-releasing peptide, ghrelin: minimal sequence of ghrelin necessary for activation of growth hormone secretagogue receptor 1a. *J Med Chem* **43**: 4370-6 [PMID:11087562]
5. Bennett KA, Langmead CJ, Wise A and Milligan G. (2009) Growth hormone secretagogues and growth hormone releasing peptides act as orthosteric super-agonists but not allosteric regulators for activation of the G protein G α (o1) by the Ghrelin receptor. *Mol Pharmacol* **76**: 802-11 [PMID:19625579]
6. Bodart V, Febbraio M, Demers A, McNicoll N, Pohankova P, Perreault A, Sejlitz T, Escher E, Silverstein RL and Lamontagne D *et al.*. (2002) CD36 mediates the cardiovascular action of growth hormone-releasing peptides in the heart. *Circ Res* **90**: 844-9 [PMID:11988484]
7. Broglio F, Boutignon F, Benso A, Gottero C, Prodam F, Arvat E, Ghé C, Catapano F, Torsello A and Locatelli V *et al.*. (2002) EP1572: a novel peptido-mimetic GH secretagogue with potent and selective GH-releasing activity in man. *J Endocrinol Invest* **25**: RC26-8 [PMID:12240910]
8. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
9. Cassoni P, Ghé C, Marrocco T, Tarabra E, Allia E, Catapano F, Deghenghi R, Ghigo E, Papotti M and Muccioli G. (2004) Expression of ghrelin and biological activity of specific receptors for ghrelin and des-acyl ghrelin in human prostate neoplasms and related cell lines. *Eur J Endocrinol* **150**: 173-84 [PMID:14763915]
10. Cassoni P, Papotti M, Catapano F, Ghé C, Deghenghi R, Ghigo E and Muccioli G. (2000) Specific binding sites for synthetic growth hormone secretagogues in non-tumoral and neoplastic human thyroid tissue. *J Endocrinol* **165**: 139-46 [PMID:10750044]
11. Cassoni P, Papotti M, Ghé C, Catapano F, Sapino A, Graziani A, Deghenghi R, Reissmann T, Ghigo E and Muccioli G. (2001) Identification, characterization, and biological activity of specific receptors for natural (ghrelin) and synthetic growth hormone secretagogues and analogs in human breast carcinomas and cell lines. *J Clin Endocrinol Metab* **86**: 1738-45 [PMID:11297611]
12. Chen CY and Tsai CY. (2012) Ghrelin and motilin in the gastrointestinal system. *Curr Pharm Des* **18**: 4755-65 [PMID:22632857]
13. Chu KM, Chow KB, Leung PK, Lau PN, Chan CB, Cheng CH and Wise H. (2007) Over-expression of the truncated ghrelin receptor polypeptide attenuates the constitutive activation of phosphatidylinositol-specific phospholipase C by ghrelin receptors but has no effect on ghrelin-stimulated extracellular signal-regulated kinase 1/2 activity. *Int J Biochem Cell Biol* **39**: 752-64 [PMID:17169600]
14. Costantini VJ, Vicentini E, Sabbatini FM, Valerio E, Lepore S, Tessari M, Sartori M, Michielin F, Melotto S and Bifone A *et al.*. (2011) GSK1614343, a novel ghrelin receptor antagonist, produces an unexpected increase of food intake and body weight in rodents and dogs. *Neuroendocrinology* **94**: 158-68 [PMID:21778696]
15. Cummings DE, Foster-Schubert KE and Overduin J. (2005) Ghrelin and energy balance: focus on current controversies. *Curr Drug Targets* **6**: 153-69 [PMID:15777186]
16. Damian M, Marie J, Leyris JP, Fehrentz JA, Verdié P, Martinez J, Banères JL and Mary S. (2012) High constitutive activity is an intrinsic feature of ghrelin receptor protein: a study with a functional monomeric GHS-R1a receptor reconstituted in lipid discs. *J Biol Chem* **287**: 3630-41 [PMID:22117076]
17. Dash PK, Karl KA, Colicos MA, Prywes R and Kandel ER. (1991) cAMP response element-binding protein is activated by Ca²⁺/calmodulin- as well as cAMP-dependent protein kinase. *Proc Natl Acad Sci USA* **88**: 5061-5 [PMID:1647024]
18. Date Y, Murakami N, Kojima M, Kuroiwa T, Matsukura S, Kangawa K and Nakazato M. (2000) Central effects of a novel acylated peptide, ghrelin, on growth hormone release in rats. *Biochem Biophys Res Commun* **275**: 477-80 [PMID:10964690]
19. Davenport AP, Bonner TI, Foord SM, Harmar AJ, Neubig RR, Pin JP, Spedding M, Kojima M and

- Kangawa K. (2005) International Union of Pharmacology. LVI. Ghrelin receptor nomenclature, distribution, and function. *Pharmacol Rev* **57**: 541-6 [PMID:16382107]
20. Dehkhoda F, Ringuet MT, Whitfield EA, Mutunduwe K, Whelan F, Nowell CJ, Misganaw D, Xu Z, Piper NBC and Clark RJ *et al.*. (2025) Constitutive ghrelin receptor activity enables reversal of dopamine D2 receptor signaling. *Mol Cell* **85**: 2246-2260.e10 [PMID:40441153]
 21. Delhanty PJ, Sun Y, Visser JA, van Kerkwijk A, Huisman M, van Ijcken WF, Swagemakers S, Smith RG, Themmen AP and van der Lely AJ. (2010) Unacylated ghrelin rapidly modulates lipogenic and insulin signaling pathway gene expression in metabolically active tissues of GHSR deleted mice. *PLoS ONE* **5**: e11749 [PMID:20668691]
 22. Depoortere I, De Winter B, Thijs T, De Man J, Pelckmans P and Peeters T. (2005) Comparison of the gastropromotory effects of ghrelin, GHRP-6 and motilin in rats in vivo and in vitro. *Eur J Pharmacol* **515**: 160-8 [PMID:15890336]
 23. Deschaine SL, Hedegaard MA, Pince CL, Farokhnia M, Moose JE, Stock IA, Adusumalli S, Akhlaghi F, Hougland JL and Sulima A *et al.*. (2023) Initial Pharmacological Characterization of a Major Hydroxy Metabolite of PF-5190457: Inverse Agonist Activity of PF-6870961 at the Ghrelin Receptor. *J Pharmacol Exp Ther* **386**: 117-128 [PMID:36631279]
 24. Dickson SL, Egecioglu E, Landgren S, Skibicka KP, Engel JA and Jerlhag E. (2011) The role of the central ghrelin system in reward from food and chemical drugs. *Mol Cell Endocrinol* **340**: 80-7 [PMID:21354264]
 25. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, Lillard JW and Taub DD. (2004) Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. *J Clin Invest* **114**: 57-66 [PMID:15232612]
 26. Dixit VD, Yang H, Cooper-Jenkins A, Giri BB, Patel K and Taub DD. (2009) Reduction of T cell-derived ghrelin enhances proinflammatory cytokine expression: implications for age-associated increases in inflammation. *Blood* **113**: 5202-5 [PMID:19324904]
 27. Druce MR, Wren AM, Park AJ, Milton JE, Patterson M, Frost G, Ghatei MA, Small C and Bloom SR. (2005) Ghrelin increases food intake in obese as well as lean subjects. *Int J Obes (Lond.)* **29**: 1130-6 [PMID:15917842]
 28. Duxbury MS, Waseem T, Ito H, Robinson MK, Zinner MJ, Ashley SW and Whang EE. (2003) Ghrelin promotes pancreatic adenocarcinoma cellular proliferation and invasiveness. *Biochem Biophys Res Commun* **309**: 464-8 [PMID:12951072]
 29. Edholm T, Levin F, Hellström PM and Schmidt PT. (2004) Ghrelin stimulates motility in the small intestine of rats through intrinsic cholinergic neurons. *Regul Pept* **121**: 25-30 [PMID:15256270]
 30. Esler WP, Rudolph J, Claus TH, Tang W, Barucci N, Brown SE, Bullock W, Daly M, Decarr L and Li Y *et al.*. (2007) Small-molecule ghrelin receptor antagonists improve glucose tolerance, suppress appetite, and promote weight loss. *Endocrinology* **148**: 5175-85 [PMID:17656463]
 31. Esposito M, Pellinen J, Kapás L and Szentirmai É. (2012) Impaired wake-promoting mechanisms in ghrelin receptor-deficient mice. *Eur J Neurosci* **35**: 233-43 [PMID:22211783]
 32. Faulkner ML, Farokhnia M, Lee MR, Farinelli L, Browning BD, Abshire K, Daurio AM, Munjal V, Deschaine SL and Boukabara SR *et al.*. (2024) A randomized, double-blind, placebo-controlled study of a GHSR blocker in people with alcohol use disorder. *JCI Insight* **9** [PMID:39704175]
 33. Feighner SD, Howard AD, Prendergast K, Palyha OC, Hreniuk DL, Nargund R, Underwood D, Tata JR, Dean DC and Tan CP *et al.*. (1998) Structural requirements for the activation of the human growth hormone secretagogue receptor by peptide and nonpeptide secretagogues. *Mol Endocrinol* **12**: 137-45 [PMID:9440817]
 34. Frascarelli S, Ghelardoni S, Ronca-Testoni S and Zucchi R. (2003) Effect of ghrelin and synthetic growth hormone secretagogues in normal and ischemic rat heart. *Basic Res Cardiol* **98**: 401-5 [PMID:14556085]
 35. Fraser GL, Hoveyda HR and Tannenbaum GS. (2008) Pharmacological demarcation of the growth hormone, gut motility and feeding effects of ghrelin using a novel ghrelin receptor agonist. *Endocrinology* **149**: 6280-8 [PMID:18719021]
 36. Fujino K, Inui A, Asakawa A, Kihara N, Fujimura M and Fujimiya M. (2003) Ghrelin induces fasted motor activity of the gastrointestinal tract in conscious fed rats. *J Physiol (Lond.)* **550**: 227-40 [PMID:12837928]
 37. Gaytan F, Morales C, Barreiro ML, Jeffery P, Chopin LK, Herington AC, Casanueva FF, Aguilar E, Dieguez C and Tena-Sempere M. (2005) Expression of growth hormone secretagogue receptor type 1a, the functional ghrelin receptor, in human ovarian surface epithelium, müllerian duct derivatives, and ovarian tumors. *J Clin Endocrinol Metab* **90**: 1798-804 [PMID:15585554]
 38. Ge X, Yang H, Bednarek MA, Galon-Tilleman H, Chen P, Chen M, Lichtman JS, Wang Y, Dalmás O and Yin Y *et al.*. (2018) LEAP2 Is an Endogenous Antagonist of the Ghrelin Receptor. *Cell Metab* **27**: 461-469.e6 [PMID:29233536]
 39. Gnanapavan S, Kola B, Bustin SA, Morris DG, McGee P, Fairclough P, Bhattacharya S, Carpenter R, Grossman AB and Korbonits M. (2002) The tissue distribution of the mRNA of

- ghrelin and subtypes of its receptor, GHS-R, in humans. *J Clin Endocrinol Metab* **87**: 2988 [PMID:12050285]
40. Gozé C, Bergé G, M'Kadmi C, Floquet N, Gagne D, Galleyrand JC, Fehrentz JA and Martinez J. (2010) Involvement of tryptophan W276 and of two surrounding amino acid residues in the high constitutive activity of the ghrelin receptor GHS-R1a. *Eur J Pharmacol* **643**: 153-61 [PMID:20599926]
 41. Gualillo O, Caminos J, Blanco M, Garcia-Caballero T, Kojima M, Kangawa K, Dieguez C and Casanueva F. (2001) Ghrelin, a novel placental-derived hormone. *Endocrinology* **142**: 788-94 [PMID:11159851]
 42. Halem HA, Taylor JE, Dong JZ, Shen Y, Datta R, Abizaid A, Diano S, Horvath T, Zizzari P and Bluet-Pajot MT *et al.*. (2004) Novel analogs of ghrelin: physiological and clinical implications. *Eur J Endocrinol* **151 Suppl 1**: S71-5 [PMID:15339248]
 43. Hansen BS, Raun K, Nielsen KK, Johansen PB, Hansen TK, Peschke B, Lau J, Andersen PH and Ankersen M. (1999) Pharmacological characterisation of a new oral GH secretagogue, NN703. *Eur J Endocrinol* **141**: 180-9 [PMID:10427162]
 44. Holliday ND, Holst B, Rodionova EA, Schwartz TW and Cox HM. (2007) Importance of constitutive activity and arrestin-independent mechanisms for intracellular trafficking of the ghrelin receptor. *Mol Endocrinol* **21**: 3100-12 [PMID:17717076]
 45. Holst B, Brandt E, Bach A, Heding A and Schwartz TW. (2005) Nonpeptide and peptide growth hormone secretagogues act both as ghrelin receptor agonist and as positive or negative allosteric modulators of ghrelin signaling. *Mol Endocrinol* **19**: 2400-11 [PMID:15905359]
 46. Holst B, Cygankiewicz A, Jensen TH, Ankersen M and Schwartz TW. (2003) High constitutive signaling of the ghrelin receptor--identification of a potent inverse agonist. *Mol Endocrinol* **17**: 2201-10 [PMID:12907757]
 47. Holst B, Frimurer TM, Mokrosinski J, Halkjaer T, Cullberg KB, Underwood CR and Schwartz TW. (2009) Overlapping binding site for the endogenous agonist, small-molecule agonists, and ago-allosteric modulators on the ghrelin receptor. *Mol Pharmacol* **75**: 44-59 [PMID:18923064]
 48. Holst B, Holliday ND, Bach A, Elling CE, Cox HM and Schwartz TW. (2004) Common structural basis for constitutive activity of the ghrelin receptor family. *J Biol Chem* **279**: 53806-17 [PMID:15383539]
 49. Holst B, Lang M, Brandt E, Bach A, Howard A, Frimurer TM, Beck-Sickinger A and Schwartz TW. (2006) Ghrelin receptor inverse agonists: identification of an active peptide core and its interaction epitopes on the receptor. *Mol Pharmacol* **70**: 936-46 [PMID:16798937]
 50. Holst B, Mokrosinski J, Lang M, Brandt E, Nygaard R, Frimurer TM, Beck-Sickinger AG and Schwartz TW. (2007) Identification of an efficacy switch region in the ghrelin receptor responsible for interchange between agonism and inverse agonism. *J Biol Chem* **282**: 15799-811 [PMID:17371869]
 51. Holst B and Schwartz TW. (2004) Constitutive ghrelin receptor activity as a signaling set-point in appetite regulation. *Trends Pharmacol Sci* **25**: 113-7 [PMID:15058279]
 52. Hosoda H, Kojima M, Matsuo H and Kangawa K. (2000) Purification and characterization of rat des-Gln14-Ghrelin, a second endogenous ligand for the growth hormone secretagogue receptor. *J Biol Chem* **275**: 21995-2000 [PMID:10801861]
 53. Howard AD, Feighner SD, Cully DF, Arena JP, Liberatore PA, Rosenblum CI, Hamelin M, Hreniuk DL, Palyha OC and Anderson J *et al.*. (1996) A receptor in pituitary and hypothalamus that functions in growth hormone release. *Science* **273**: 974-7 [PMID:8688086]
 54. Jiang H, Betancourt L and Smith RG. (2006) Ghrelin amplifies dopamine signaling by cross talk involving formation of growth hormone secretagogue receptor/dopamine receptor subtype 1 heterodimers. *Mol Endocrinol* **20**: 1772-85 [PMID:16601073]
 55. Kageyama H, Funahashi H, Hirayama M, Takenoya F, Kita T, Kato S, Sakurai J, Lee EY, Inoue S and Date Y *et al.*. (2005) Morphological analysis of ghrelin and its receptor distribution in the rat pancreas. *Regul Pept* **126**: 67-71 [PMID:15620416]
 56. Karasawa H, Pietra C, Giuliano C, Garcia-Rubio S, Xu X, Yakabi S, Taché Y and Wang L. (2014) New ghrelin agonist, HM01 alleviates constipation and L-dopa-delayed gastric emptying in 6-hydroxydopamine rat model of Parkinson's disease. *Neurogastroenterol Motil* **26**: 1771-82 [PMID:25327342]
 57. Katugampola SD, Pallikaros Z and Davenport AP. (2001) [125I-His(9)]-ghrelin, a novel radioligand for localizing GHS orphan receptors in human and rat tissue: up-regulation of receptors with atherosclerosis. *Br J Pharmacol* **134**: 143-9 [PMID:11522606]
 58. Kern A, Albarran-Zeckler R, Walsh HE and Smith RG. (2012) Apo-ghrelin receptor forms heteromers with DRD2 in hypothalamic neurons and is essential for anorexigenic effects of DRD2 agonism. *Neuron* **73**: 317-32 [PMID:22284186]
 59. Kleinz MJ, Kuc RE, Maguire JJ and Davenport AP. Endogenous vasodilator ghrelin and its growth hormone secretagogue receptor 1a (GHS-R1a) immunocytochemically localize to endothelial cells within the human vasculature. <http://www.pa2online.org/scripts/relatedVol1Issue3.asp>. Accessed on 05/05/2015.

60. Kobelt P, Tebbe JJ, Tjandra I, Stengel A, Bae HG, Andresen V, van der Voort IR, Veh RW, Werner CR and Klapp BF *et al.* (2005) CCK inhibits the orexigenic effect of peripheral ghrelin. *Am J Physiol Regul Integr Comp Physiol* **288**: R751-8 [PMID:15550621]
61. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H and Kangawa K. (1999) Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* **402**: 656-60 [PMID:10604470]
62. Kojima M and Kangawa K. (2005) Ghrelin: structure and function. *Physiol Rev* **85**: 495-522 [PMID:15788704]
63. Kong J, Chuddy J, Stock IA, Loria PM, Straub SV, Vage C, Cameron KO, Bhattacharya SK, Lapham K and McClure KF *et al.* (2016) Pharmacological characterization of the first in class clinical candidate PF-05190457: a selective ghrelin receptor competitive antagonist with inverse agonism that increases vagal afferent firing and glucose-dependent insulin secretion ex vivo. *Br J Pharmacol* **173**: 1452-64 [PMID:26784385]
64. Korbonits M, Kojima M, Kangawa K and Grossman AB. (2001) Presence of ghrelin in normal and adenomatous human pituitary. *Endocrine* **14**: 101-4 [PMID:11322490]
65. Lai JK, Cheng CH, Ko WH and Leung PS. (2005) Ghrelin system in pancreatic AR42J cells: its ligand stimulation evokes calcium signalling through ghrelin receptors. *Int J Biochem Cell Biol* **37**: 887-900 [PMID:15694847]
66. Li GZ, Jiang W, Zhao J, Pan CS, Cao J, Tang CS and Chang L. (2005) Ghrelin blunted vascular calcification in vivo and in vitro in rats. *Regul Pept* **129**: 167-76 [PMID:15927713]
67. Li WG, Gavrilu D, Liu X, Wang L, Gunnlaugsson S, Stoll LL, McCormick ML, Sigmund CD, Tang C and Weintraub NL. (2004) Ghrelin inhibits proinflammatory responses and nuclear factor-kappaB activation in human endothelial cells. *Circulation* **109**: 2221-6 [PMID:15117840]
68. Lin L, Saha PK, Ma X, Henshaw IO, Shao L, Chang BH, Buras ED, Tong Q, Chan L and McGuinness OP *et al.* (2011) Ablation of ghrelin receptor reduces adiposity and improves insulin sensitivity during aging by regulating fat metabolism in white and brown adipose tissues. *Aging Cell* **10**: 996-1010 [PMID:21895961]
69. Lin Y, Matsumura K, Fukuhara M, Kagiya S, Fujii K and Iida M. (2004) Ghrelin acts at the nucleus of the solitary tract to decrease arterial pressure in rats. *Hypertension* **43**: 977-82 [PMID:14993197]
70. Longo KA, Charoenthongtrakul S, Giuliana DJ, Govek EK, McDonagh T, Qi Y, DiStefano PS and Geddes BJ. (2008) Improved insulin sensitivity and metabolic flexibility in ghrelin receptor knockout mice. *Regul Pept* **150**: 55-61 [PMID:18453014]
71. M'Kadmi C, Cabral A, Barrile F, Giribaldi J, Cantel S, Damian M, Mary S, Denoyelle S, Dutertre S and Peraldi-Roux S *et al.* (2019) N-Terminal Liver-Expressed Antimicrobial Peptide 2 (LEAP2) Region Exhibits Inverse Agonist Activity toward the Ghrelin Receptor. *J Med Chem* **62**: 965-973 [PMID:30543423]
72. Ma X, Lin Y, Lin L, Qin G, Pereira FA, Haymond MW, Butte NF and Sun Y. (2012) Ablation of ghrelin receptor in leptin-deficient ob/ob mice has paradoxical effects on glucose homeostasis when compared with ablation of ghrelin in ob/ob mice. *Am J Physiol Endocrinol Metab* **303**: E422-31 [PMID:22669248]
73. Malcolm JA and Sutherland DC. (1991) HIV and nutrition. *Lancet* **338**: 760 [PMID:1679893]
74. Mani BK, Puzziferri N, He Z, Rodriguez JA, Osborne-Lawrence S, Metzger NP, Chhina N, Gaylinn B, Thorner MO and Thomas EL *et al.* (2019) LEAP2 changes with body mass and food intake in humans and mice. *J Clin Invest* **129**: 3909-3923 [PMID:31424424]
75. Mary S, Damian M, Louet M, Floquet N, Fehrentz JA, Marie J, Martinez J and Banères JL. (2012) Ligands and signaling proteins govern the conformational landscape explored by a G protein-coupled receptor. *Proc Natl Acad Sci USA* **109**: 8304-9 [PMID:22573814]
76. Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z, Hosoda H, Kojima M and Kangawa K. (2000) Ghrelin stimulates gastric acid secretion and motility in rats. *Biochem Biophys Res Commun* **276**: 905-8 [PMID:11027567]
77. Matsumoto M, Hosoda H, Kitajima Y, Morozumi N, Minamitake Y, Tanaka S, Matsuo H, Kojima M, Hayashi Y and Kangawa K. (2001) Structure-activity relationship of ghrelin: pharmacological study of ghrelin peptides. *Biochem Biophys Res Commun* **287**: 142-6 [PMID:11549267]
78. McKee KK, Palyha OC, Feighner SD, Hreniuk DL, Tan CP, Phillips MS, Smith RG, Van der Ploeg LH and Howard AD. (1997) Molecular analysis of rat pituitary and hypothalamic growth hormone secretagogue receptors. *Mol Endocrinol* **11**: 415-23 [PMID:9092793]
79. Mende F, Hundahl C, Plouffe B, Skov LJ, Sivertsen B, Madsen AN, Lückmann M, Diep TA, Offermanns S and Frimurer TM *et al.* (2018) Translating biased signaling in the ghrelin receptor system into differential in vivo functions. *Proc Natl Acad Sci U S A* **115**: E10255-E10264 [PMID:30301804]
80. Mokrosiński J, Frimurer TM, Sivertsen B, Schwartz TW and Holst B. (2012) Modulation of constitutive activity and signaling bias of the ghrelin receptor by conformational constraint in the second extracellular loop. *J Biol Chem* **287**: 33488-502 [PMID:22846991]
81. Mondal MS, Date Y, Yamaguchi H, Toshinai K, Tsuruta T, Kangawa K and Nakazato M. (2005)

Identification of ghrelin and its receptor in neurons of the rat arcuate nucleus. *Regul Pept* **126**: 55-9 [PMID:15620414]

82. Moulin A, Brunel L, Boeglin D, Demange L, Ryan J, M'Kadmi C, Denoyelle S, Martinez J and Fehrentz JA. (2013) The 1,2,4-triazole as a scaffold for the design of ghrelin receptor ligands: development of JMV 2959, a potent antagonist. *Amino Acids* **44**: 301-14 [PMID:22798076]
83. Moulin A, Demange L, Bergé G, Gagne D, Ryan J, Mousseaux D, Heitz A, Perrissoud D, Locatelli V and Torsello A *et al.*. (2007) Toward potent ghrelin receptor ligands based on trisubstituted 1,2,4-triazole structure. 2. Synthesis and pharmacological in vitro and in vivo evaluations. *J Med Chem* **50**: 5790-806 [PMID:17927165]
84. Mousseaux D, Le Gallic L, Ryan J, Oiry C, Gagne D, Fehrentz JA, Galleyrand JC and Martinez J. (2006) Regulation of ERK1/2 activity by ghrelin-activated growth hormone secretagogue receptor 1A involves a PLC/PKCvarepsilon pathway. *Br J Pharmacol* **148**: 350-65 [PMID:16582936]
85. Muccioli G, Papotti M, Locatelli V, Ghigo E and Deghenghi R. (2001) Binding of 125I-labeled ghrelin to membranes from human hypothalamus and pituitary gland. *J Endocrinol Invest* **24**: RC7-9 [PMID:11314756]
86. Nagaya N and Kangawa K. (2003) Ghrelin, a novel growth hormone-releasing peptide, in the treatment of chronic heart failure. *Regul Pept* **114**: 71-7 [PMID:12832093]
87. Nagaya N and Kangawa K. (2003) Ghrelin improves left ventricular dysfunction and cardiac cachexia in heart failure. *Curr Opin Pharmacol* **3**: 146-51 [PMID:12681236]
88. Nagaya N, Kojima M and Kangawa K. (2006) Ghrelin, a novel growth hormone-releasing peptide, in the treatment of cardiopulmonary-associated cachexia. *Intern Med* **45**: 127-34 [PMID:16508225]
89. Nagaya N, Kojima M, Uematsu M, Yamagishi M, Hosoda H, Oya H, Hayashi Y and Kangawa K. (2001) Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. *Am J Physiol Regul Integr Comp Physiol* **280**: R1483-7 [PMID:11294772]
90. Nagaya N, Miyatake K, Uematsu M, Oya H, Shimizu W, Hosoda H, Kojima M, Nakanishi N, Mori H and Kangawa K. (2001) Hemodynamic, renal, and hormonal effects of ghrelin infusion in patients with chronic heart failure. *J Clin Endocrinol Metab* **86**: 5854-9 [PMID:11739451]
91. Nagaya N, Uematsu M, Kojima M, Ikeda Y, Yoshihara F, Shimizu W, Hosoda H, Hirota Y, Ishida H and Mori H *et al.*. (2001) Chronic administration of ghrelin improves left ventricular dysfunction and attenuates development of cardiac cachexia in rats with heart failure. *Circulation* **104**: 1430-5 [PMID:11560861]
92. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K and Matsukura S. (2001) A role for ghrelin in the central regulation of feeding. *Nature* **409**: 194-8 [PMID:11196643]
93. Okumura H, Nagaya N, Enomoto M, Nakagawa E, Oya H and Kangawa K. (2002) Vasodilatory effect of ghrelin, an endogenous peptide from the stomach. *J Cardiovasc Pharmacol* **39**: 779-783 [PMID:12021570]
94. Palus S, Schur R, Akashi YJ, Bockmeyer B, Datta R, Halem H, Dong J, Culler MD, Adams V and Anker SD *et al.*. (2011) Ghrelin and its analogues, BIM-28131 and BIM-28125, improve body weight and regulate the expression of MuRF-1 and MAFbx in a rat heart failure model. *PLoS ONE* **6**: e26865 [PMID:22102869]
95. Palyha OC, Feighner SD, Tan CP, McKee KK, Hreniuk DL, Gao YD, Schleim KD, Yang L, Morriello GJ and Nargund R *et al.*. (2000) Ligand activation domain of human orphan growth hormone (GH) secretagogue receptor (GHS-R) conserved from Pufferfish to humans. *Mol Endocrinol* **14**: 160-9 [PMID:10628755]
96. Pantel J, Legendre M, Cabrol S, Hilal L, Hajaji Y, Morisset S, Nivot S, Vie-Luton MP, Grouselle D and de Kerdanet M *et al.*. (2006) Loss of constitutive activity of the growth hormone secretagogue receptor in familial short stature. *J Clin Invest* **116**: 760-8 [PMID:16511605]
97. Papotti M, Ghè C, Cassoni P, Catapano F, Deghenghi R, Ghigo E and Muccioli G. (2000) Growth hormone secretagogue binding sites in peripheral human tissues. *J Clin Endocrinol Metab* **85**: 3803-7 [PMID:11061542]
98. Pawson AJ, Faccenda E, Maudsley S, Lu ZL, Naor Z and Millar RP. (2008) Mammalian type I gonadotropin-releasing hormone receptors undergo slow, constitutive, agonist-independent internalization. *Endocrinology* **149**: 1415-22 [PMID:18039780]
99. Peeters TL. (2003) Central and peripheral mechanisms by which ghrelin regulates gut motility. *J Physiol Pharmacol* **54 Suppl 4**: 95-103 [PMID:15075452]
100. Peino R, Baldelli R, Rodriguez-Garcia J, Rodriguez-Segade S, Kojima M, Kangawa K, Arvat E, Ghigo E, Dieguez C and Casanueva FF. (2000) Ghrelin-induced growth hormone secretion in humans. *Eur J Endocrinol* **143**: R11-4 [PMID:11124868]
101. Perdonà E, Faggioni F, Buson A, Sabbatini FM, Corti C and Corsi M. (2011) Pharmacological characterization of the ghrelin receptor antagonist, GSK1614343 in rat RC-4B/C cells natively expressing GHS type 1a receptors. *Eur J Pharmacol* **650**: 178-83 [PMID:21034740]
102. Pettersson I, Muccioli G, Granata R, Deghenghi R, Ghigo E, Ohlsson C and Isgaard J. (2002) Natural (ghrelin) and synthetic (hexarelin) GH secretagogues stimulate H9c2 cardiomyocyte cell

- proliferation. *J Endocrinol* **175**: 201-9 [PMID:12379504]
103. Pfluger PT, Kirchner H, Günzel S, Schrott B, Perez-Tilve D, Fu S, Benoit SC, Horvath T, Joost HG and Wortley KE *et al.*. (2008) Simultaneous deletion of ghrelin and its receptor increases motor activity and energy expenditure. *Am J Physiol Gastrointest Liver Physiol* **294**: G610-8 [PMID:18048479]
 104. Pietra C, Takeda Y, Tazawa-Ogata N, Minami M, Yuanfeng X, Duus EM and Northrup R. (2014) Anamorelin HCl (ONO-7643), a novel ghrelin receptor agonist, for the treatment of cancer anorexia-cachexia syndrome: preclinical profile. *J Cachexia Sarcopenia Muscle* **5**: 329-37 [PMID:25267366]
 105. Poitras P and Peeters TL. (2008) Motilin. *Curr Opin Endocrinol Diabetes Obes* **15**: 54-7 [PMID:18185063]
 106. Rediger A, Piechowski CL, Habegger K, Grüters A, Krude H, Tschöp MH, Kleinau G and Biebermann H. (2012) MC4R dimerization in the paraventricular nucleus and GHSR/MC3R heterodimerization in the arcuate nucleus: is there relevance for body weight regulation? *Neuroendocrinology* **95**: 277-88 [PMID:22327910]
 107. Rudolph J, Esler WP, O'connor S, Coish PD, Wickens PL, Brands M, Bierer DE, Bloomquist BT, Bondar G and Chen L *et al.*. (2007) Quinazolinone derivatives as orally available ghrelin receptor antagonists for the treatment of diabetes and obesity. *J Med Chem* **50**: 5202-16 [PMID:17887659]
 108. Sabbatini FM, Di Fabio R, Corsi M, Cavanni P, Bromidge SM, St-Denis Y, D'Adamo L, Contini S, Rinaldi M and Guery S *et al.*. (2010) Discovery process and characterization of novel carbohydrazide derivatives as potent and selective GHSR1a antagonists. *ChemMedChem* **5**: 1450-5 [PMID:20593439]
 109. Schellekens H, van Oeffelen WE, Dinan TG and Cryan JF. (2013) Promiscuous dimerization of the growth hormone secretagogue receptor (GHS-R1a) attenuates ghrelin-mediated signaling. *J Biol Chem* **288**: 181-91 [PMID:23161547]
 110. Shin YK, Martin B, Kim W, White CM, Ji S, Sun Y, Smith RG, Sévigny J, Tschöp MH and Maudsley S *et al.*. (2010) Ghrelin is produced in taste cells and ghrelin receptor null mice show reduced taste responsiveness to salty (NaCl) and sour (citric acid) tastants. *PLoS ONE* **5**: e12729 [PMID:20856820]
 111. Shuto Y, Shibasaki T, Otagiri A, Kuriyama H, Ohata H, Tamura H, Kamegai J, Sugihara H, Oikawa S and Wakabayashi I. (2002) Hypothalamic growth hormone secretagogue receptor regulates growth hormone secretion, feeding, and adiposity. *J Clin Invest* **109**: 1429-36 [PMID:12045256]
 112. Sivertsen B, Holliday N, Madsen AN and Holst B. (2013) Functionally biased signalling properties of 7TM receptors - opportunities for drug development for the ghrelin receptor. *Br J Pharmacol* **170**: 1349-62 [PMID:24032557]
 113. Sivertsen B, Lang M, Frimurer TM, Holliday ND, Bach A, Els S, Engelstoft MS, Petersen PS, Madsen AN and Schwartz TW *et al.*. (2011) Unique interaction pattern for a functionally biased ghrelin receptor agonist. *J Biol Chem* **286**: 20845-60 [PMID:21402696]
 114. Smith RG, Cheng K, Schoen WR, Pong SS, Hickey G, Jacks T, Butler B, Chan WW, Chaung LY and Judith F *et al.*. (1993) A nonpeptidyl growth hormone secretagogue. *Science* **260**: 1640-3 [PMID:8503009]
 115. Stevens T and Parsi MA. (2010) Endoscopic ultrasound for the diagnosis of chronic pancreatitis. *World J Gastroenterol* **16**: 2841-50 [PMID:20556829]
 116. Sun Y, Butte NF, Garcia JM and Smith RG. (2008) Characterization of adult ghrelin and ghrelin receptor knockout mice under positive and negative energy balance. *Endocrinology* **149**: 843-50 [PMID:18006636]
 117. Sun Y, Wang P, Zheng H and Smith RG. (2004) Ghrelin stimulation of growth hormone release and appetite is mediated through the growth hormone secretagogue receptor. *Proc Natl Acad Sci USA* **101**: 4679-84 [PMID:15070777]
 118. Takaya K, Ariyasu H, Kanamoto N, Iwakura H, Yoshimoto A, Harada M, Mori K, Komatsu Y, Usui T and Shimatsu A *et al.*. (2000) Ghrelin strongly stimulates growth hormone release in humans. *J Clin Endocrinol Metab* **85**: 4908-11 [PMID:11134161]
 119. Tanaka M, Hayashida Y, Iguchi N, Nakao N, Nakai N and Nakashima K. (2001) Organization of the mouse ghrelin gene and promoter: occurrence of a short noncoding first exon. *Endocrinology* **142**: 3697-700 [PMID:11459820]
 120. Theander-Carrillo C, Wiedmer P, Cettour-Rose P, Nogueiras R, Perez-Tilve D, Pfluger P, Castaneda TR, Muzzin P, Schürmann A and Szanto I *et al.*. (2006) Ghrelin action in the brain controls adipocyte metabolism. *J Clin Invest* **116**: 1983-93 [PMID:16767221]
 121. Thompson NM, Gill DA, Davies R, Loveridge N, Houston PA, Robinson IC and Wells T. (2004) Ghrelin and des-octanoyl ghrelin promote adipogenesis directly in vivo by a mechanism independent of the type 1a growth hormone secretagogue receptor. *Endocrinology* **145**: 234-42 [PMID:14551228]
 122. Tokunaga T, Hume WE, Umezome T, Okazaki K, Ueki Y, Kumagai K, Hourai S, Nagamine J, Seki

- H and Taiji M *et al.* (2001) Oxindole derivatives as orally active potent growth hormone secretagogues. *J Med Chem* **44**: 4641-9 [PMID:11741481]
123. Tolle V, Zizzari P, Tomasetto C, Rio MC, Epelbaum J and Bluet-Pajot MT. (2001) In vivo and in vitro effects of ghrelin/motilin-related peptide on growth hormone secretion in the rat. *Neuroendocrinology* **73**: 54-61 [PMID:11174017]
 124. Tschöp M, Smiley DL and Heiman ML. (2000) Ghrelin induces adiposity in rodents. *Nature* **407**: 908-13 [PMID:11057670]
 125. Tsubota Y, Owada-Makabe K, Yukawa K and Maeda M. (2005) Hypotensive effect of des-acyl ghrelin at nucleus tractus solitarii of rat. *Neuroreport* **16**: 163-6 [PMID:15671869]
 126. Valentin-Hansen L, Holst B, Frimurer TM and Schwartz TW. (2012) PheVI:09 (Phe6.44) as a sliding microswitch in seven-transmembrane (7TM) G protein-coupled receptor activation. *J Biol Chem* **287**: 43516-26 [PMID:23135271]
 127. van der Lely AJ, Tschöp M, Heiman ML and Ghigo E. (2004) Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. *Endocr Rev* **25**: 426-57 [PMID:15180951]
 128. Verhulst PJ, De Smet B, Saels I, Thijs T, Ver Donck L, Moechars D, Peeters TL and Depoortere I. (2008) Role of ghrelin in the relationship between hyperphagia and accelerated gastric emptying in diabetic mice. *Gastroenterology* **135**: 1267-76 [PMID:18657539]
 129. Volante M, Allia E, Fulcheri E, Cassoni P, Ghigo E, Muccioli G and Papotti M. (2003) Ghrelin in fetal thyroid and follicular tumors and cell lines: expression and effects on tumor growth. *Am J Pathol* **162**: 645-54 [PMID:12547722]
 130. Wakabayashi H, Arai H and Inui A. (2021) The regulatory approval of anamorelin for treatment of cachexia in patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer in Japan: facts and numbers. *J Cachexia Sarcopenia Muscle* **12**: 14-16 [PMID:33382205]
 131. Weber J, Staerz E, Mettang T, Machleidt C and Kuhlmann U. (1989) Treatment of peritonitis in continuous ambulatory peritoneal dialysis (CAPD) with intraperitoneal cefazolin and gentamicin. *Perit Dial Int* **9**: 191-5 [PMID:2488364]
 132. Wierup N, Svensson H, Mulder H and Sundler F. (2002) The ghrelin cell: a novel developmentally regulated islet cell in the human pancreas. *Regul Pept* **107**: 63-9 [PMID:12137967]
 133. Wiley KE and Davenport AP. (2002) Comparison of vasodilators in human internal mammary artery: ghrelin is a potent physiological antagonist of endothelin-1. *Br J Pharmacol* **136**: 1146-52 [PMID:12163347]
 134. Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, Dhillo WS, Ghatei MA and Bloom SR. (2001) Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab* **86**: 5992 [PMID:11739476]
 135. Wren AM, Small CJ, Ward HL, Murphy KG, Dakin CL, Taheri S, Kennedy AR, Roberts GH, Morgan DG and Ghatei MA *et al.* (2000) The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. *Endocrinology* **141**: 4325-8 [PMID:11089570]
 136. Xin Z, Serby MD, Zhao H, Kosogof C, Szczepankiewicz BG, Liu M, Liu B, Hutchins CW, Sarris KA and Hoff ED *et al.* (2006) Discovery and pharmacological evaluation of growth hormone secretagogue receptor antagonists. *J Med Chem* **49**: 4459-69 [PMID:16854051]
 137. Xu L, Depoortere I, Tomasetto C, Zandecki M, Tang M, Timmermans JP and Peeters TL. (2005) Evidence for the presence of motilin, ghrelin, and the motilin and ghrelin receptor in neurons of the myenteric plexus. *Regul Pept* **124**: 119-25 [PMID:15544849]
 138. Yang J, Brown MS, Liang G, Grishin NV and Goldstein JL. (2008) Identification of the acyltransferase that octanoylates ghrelin, an appetite-stimulating peptide hormone. *Cell* **132**: 387-96 [PMID:18267071]
 139. Yasuda T, Masaki T, Kakuma T and Yoshimatsu H. (2003) Centrally administered ghrelin suppresses sympathetic nerve activity in brown adipose tissue of rats. *Neurosci Lett* **349**: 75-8 [PMID:12946556]
 140. Zigman JM, Jones JE, Lee CE, Saper CB and Elmquist JK. (2006) Expression of ghrelin receptor mRNA in the rat and the mouse brain. *J Comp Neurol* **494**: 528-48 [PMID:16320257]
 141. Zigman JM, Nakano Y, Coppari R, Balthasar N, Marcus JN, Lee CE, Jones JE, Deysher AE, Waxman AR and White RD *et al.* (2005) Mice lacking ghrelin receptors resist the development of diet-induced obesity. *J Clin Invest* **115**: 3564-72 [PMID:16322794]