

Gonadotrophin-releasing hormone receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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Abstract

GnRH₁ and GnRH₂ receptors (**provisonal nomenclature** [35], also called Type I and Type II GnRH receptor, respectively [78]) have been cloned from numerous species, most of which express two or three types of GnRH receptor [78, 77, 107]. GnRH I (p-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂) is a hypothalamic decapeptide also known as luteinizing hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin or simply as GnRH. It is a member of a family of similar peptides found in many species [78, 77, 107] including GnRH II (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-NH₂ (which is also known as chicken GnRH-II). Receptors for three forms of GnRH exist in some species but only GnRH I and GnRH II and their cognate receptors have been found in mammals [78, 77, 107]. GnRH₁ receptors are expressed by pituitary gonadotrophs, where they mediate the effects of GnRH on gonadotropin hormone synthesis and secretion that underpin central control of mammalian reproduction. GnRH analogues are used in assisted reproduction and to treat steroid hormone-dependent conditions [53]. Notably, agonists cause desensitization of GnRH-stimulated gonadotropin secretion and the consequent reduction in circulating sex steroids is exploited to treat hormone-dependent cancers of the breast, ovary and prostate [53]. GnRH₁ receptors are selectively activated by GnRH I and all lack the COOH-terminal tails found in other GPCRs. GnRH₂ receptors do have COOH-terminal tails and (where tested) are selective for GnRH II over GnRH I. GnRH₂ receptors are expressed by some primates but not by humans [81]. Phylogenetic classifications divide GnRH receptors into three [78] or five groups [122] and highlight examples of gene loss through evolution, with humans retaining only one ancient gene.

Contents

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Introduction to Gonadotrophin-releasing hormone receptors

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Receptors

GnRH₁ receptor

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GnRH₂ receptor

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=257>

References

1. Anderes KL, Luthin DR, Castillo R, Kraynov EA, Castro M, Nared-Hood K, Gregory ML, Pathak VP, Christie LC and Paderes G *et al.* (2003) Biological characterization of a novel, orally active small molecule gonadotropin-releasing hormone (GnRH) antagonist using castrated and intact rats. *J. Pharmacol. Exp. Ther.* **305**: 688-95 [PMID:12606616]
2. Anderson L, Hillier SG, Eidne KA and Miro F. (1996) GnRH-induced calcium mobilisation and inositol phosphate production in immature and mature rat ovarian granulosa cells. *J Endocrinol* **149**: 449-456 [PMID:8691103]
3. Anderson L, McGregor A, Cook JV, Chilvers E and Eidne KA. (1995) Rapid desensitization of GnRH-stimulated intracellular signalling events in alpha T3-1 and HEK-293 cells expressing the GnRH receptor. *Endocrinology* **136**: 5228-31 [PMID:7588262]
4. Anderson L, Milligan G and Eidne KA. (1993) Characterization of the gonadotrophin-releasing hormone receptor in alpha T3-1 pituitary gonadotroph cells. *J Endocrinol* **136**: 51-58 [PMID:8381456]
5. Ashton WT, Sisco RM, Kieczkowski GR, Yang YT, Yudkovitz JB, Cui J, Mount GR, Ren RN, Wu TJ and Shen X *et al.* (2001) Orally bioavailable, indole-based nonpeptide GnRH receptor antagonists with high potency and functional activity. *Bioorg. Med. Chem. Lett.* **11**: 2597-602 [PMID:11551758]
6. Beckers T, Bernd M, Kutscher B, Kühne R, Hoffmann S and Reissmann T. (2001) Structure-function studies of linear and cyclized peptide antagonists of the GnRH receptor. *Biochem. Biophys. Res. Commun.* **289**: 653-63 [PMID:11726197]
7. Beckers T, Marheineke K, Reiländer H and Hilgard P. (1995) Selection and characterization of mammalian cell lines with stable over-expression of human pituitary receptors for gonadoliberin. *Eur. J. Biochem.* **231**: 535-43 [PMID:7649152]
8. Beckers T, Reiländer H and Hilgard P. (1997) Characterization of gonadotropin-releasing hormone analogs based on a sensitive cellular luciferase reporter gene assay. *Anal. Biochem.* **251**: 17-23 [PMID:9300077]
9. Betz SF, Zhu YF, Chen C and Struthers RS. (2008) Non-peptide gonadotropin-releasing hormone receptor antagonists. *J Med Chem* **51**: 3331-3348 [PMID:18419112]
10. Bédécarrats GY and Kaiser UB. (2007) Mutations in the human gonadotropin-releasing hormone receptor: insights into receptor biology and function. *Semin. Reprod. Med.* **25**: 368-78 [PMID:17710733]
11. Caunt CJ, Hislop JN, Kelly E, Matharu AL, Green LD, Sedgley KR, Finch AR and McArdle CA. (2004) Regulation of gonadotropin-releasing hormone receptors by protein kinase C: inside out signalling and evidence for multiple active conformations. *Endocrinology* **145**: 3594-602 [PMID:15059960]
12. Caunt CJ, Perett RM, Fowkes RC and McArdle CA. (2012) Mechanisms of GnRH-induced extracellular

- signal-regulated kinase nuclear localization. *PLoS ONE* **7**: e40077 [PMID:22808094]
13. Chen C, Wu D, Guo Z, Xie Q, Reinhart GJ, Madan A, Wen J, Chen T, Huang CQ and Chen M *et al.*. (2008) Discovery of sodium R-(+)-4-[2-[5-(2-fluoro-3-methoxyphenyl)-3-(2-fluoro-6-[trifluoromethyl]benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenylethylamino]butyrate (elagolix), a potent and orally available nonpeptide antagonist of the human gonadotropin-releasing hormone receptor. *J. Med. Chem.* **51**: 7478-85 [PMID:19006286]
 14. Chen HF, Jeung EB, Stephenson M and Leung PC. (1999) Human peripheral blood mononuclear cells express gonadotropin-releasing hormone (GnRH), GnRH receptor, and interleukin-2 receptor gamma-chain messenger ribonucleic acids that are regulated by GnRH in vitro. *J. Clin. Endocrinol. Metab.* **84**: 743-50 [PMID:10022447]
 15. Cheng CK and Leung PC. (2005) Molecular biology of gonadotropin-releasing hormone (GnRH)-I, GnRH-II, and their receptors in humans. *Endocr. Rev.* **26**: 283-306 [PMID:15561800]
 16. Chevrier L, Guimiot F and de Roux N. (2011) GnRH receptor mutations in isolated gonadotropic deficiency. *Mol. Cell. Endocrinol.* **346**: 21-8 [PMID:21645587]
 17. Chi L, Zhou W, Prikhozhan A, Flanagan C, Davidson JS, Golembos M, Illing N, Millar RP and Sealfon SC. (1993) Cloning and characterization of the human GnRH receptor. *Mol. Cell. Endocrinol.* **91**: R1-6 [PMID:8386108]
 18. Cho N, Harada M, Imaeda T, Imada T, Matsumoto H, Hayase Y, Sasaki S, Furuya S, Suzuki N and Okubo S *et al.*. (1998) Discovery of a novel, potent, and orally active nonpeptide antagonist of the human luteinizing hormone-releasing hormone (LHRH) receptor. *J. Med. Chem.* **41**: 4190-5 [PMID:9784092]
 19. Clayton RN, Solano AR, Garcia-Vela A, Dufau ML and Catt KJ. (1980) Regulation of pituitary receptors for gonadotropin-releasing hormone during the rat estrous cycle. *Endocrinology* **107**: 699-706 [PMID:6249571]
 20. Conn PM and Crowley Jr WF. (1994) Gonadotropin-releasing hormone and its analogs. *Annu. Rev. Med.* **45**: 391-405 [PMID:8198390]
 21. Conn PM, Rogers DC and McNeil R. (1982) Potency enhancement of a GnRH agonist: GnRH-receptor microaggregation stimulates gonadotropin release. *Endocrinology* **111**: 335-7 [PMID:6282571]
 22. Conn PM and Ulloa-Aguirre A. (2011) Pharmacological chaperones for misfolded gonadotropin-releasing hormone receptors. *Adv. Pharmacol.* **62**: 109-41 [PMID:21907908]
 23. Conne BS, Scaglioni S, Lang U, Sizonenko PC and Aubert ML. (1982) Pituitary receptor sites for gonadotropin-releasing hormone: effect of castration and substitutive therapy with sex steroids in the male rat. *Endocrinology* **110**: 70-79 [PMID:6274626]
 24. Delahaye R, Manna PR, Bérault A, Berreur-Bonnenfant J, Berreur P and Counis R. (1997) Rat gonadotropin-releasing hormone receptor expressed in insect cells induces activation of adenylyl cyclase. *Mol. Cell. Endocrinol.* **135**: 119-27 [PMID:9484907]
 25. DeVita RJ, Walsh TF, Young JR, Jiang J, Ujjainwalla F, Toupence RB, Parikh M, Huang SX, Fair JA and Goulet MT *et al.*. (2001) A potent, nonpeptidyl 1H-quinolone antagonist for the gonadotropin-releasing hormone receptor. *J. Med. Chem.* **44**: 917-22 [PMID:11300873]
 26. Dong F, Skinner DC, Wu TJ and Ren J. (2011) The heart: a novel gonadotrophin-releasing hormone target. *J. Neuroendocrinol.* **23**: 456-63 [PMID:21332841]
 27. Eidne KA, Sellar RE, Couper G, Anderson L and Taylor PL. (1992) Molecular cloning and characterisation of the rat pituitary gonadotropin-releasing hormone (GnRH) receptor. *Mol. Cell. Endocrinol.* **90**: R5-9 [PMID:1338727]
 28. Engel JB, Hahne JC, Häusler SF, Meyer S, Segerer SE, Diessner J, Dietl J and Honig A. (2012) Peptidomimetic GnRH antagonist AEZS-115 inhibits the growth of ovarian and endometrial cancer cells. *Anticancer Res.* **32**: 2063-8 [PMID:22593489]
 29. Engel JB and Schally AV. (2007) Drug Insight: clinical use of agonists and antagonists of luteinizing-hormone-releasing hormone. *Nat Clin Pract Endocrinol Metab* **3**: 157-67 [PMID:17237842]
 30. Fan NC, Jeung EB, Peng C, Olofsson JI, Krisinger J and Leung PC. (1994) The human gonadotropin-releasing hormone (GnRH) receptor gene: cloning, genomic organization and chromosomal assignment.

- Mol. Cell. Endocrinol.* **103**: R1-6 [PMID:7958384]
31. Fan NC, Peng C, Krisinger J and Leung PC. (1995) The human gonadotropin-releasing hormone receptor gene: complete structure including multiple promoters, transcription initiation sites, and polyadenylation signals. *Mol. Cell. Endocrinol.* **107**: R1-8 [PMID:7768323]
 32. Finch AR, Caunt CJ, Armstrong SP and McArdle CA. (2010) Plasma membrane expression of gonadotropin-releasing hormone receptors: regulation by peptide and nonpeptide antagonists. *Mol. Endocrinol.* **24**: 423-35 [PMID:20009083]
 33. Finch AR, Sedgley KR, Armstrong SP, Caunt CJ and McArdle CA. (2010) Trafficking and signalling of gonadotrophin-releasing hormone receptors: an automated imaging approach. *Br. J. Pharmacol.* **159**: 751-60 [PMID:19888967]
 34. Fister S, Günther AR, Aicher B, Paulini KW, Emons G and Gründker C. (2009) GnRH-II antagonists induce apoptosis in human endometrial, ovarian, and breast cancer cells via activation of stress-induced MAPKs p38 and JNK and proapoptotic protein Bax. *Cancer Res.* **69**: 6473-81 [PMID:19638591]
 35. Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M and Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol. Rev.* **57**: 279-88 [PMID:15914470]
 36. Fromme BJ, Katz AA, Roeske RW, Millar RP and Flanagan CA. (2001) Role of aspartate7.32(302) of the human gonadotropin-releasing hormone receptor in stabilizing a high-affinity ligand conformation. *Mol Pharmacol* **60**: 1280-1287 [PMID:11723235]
 37. Grosse R, Schmid A, Schöneberg T, Herrlich A, Muhn P, Schultz G and Gudermann T. (2000) Gonadotropin-releasing hormone receptor initiates multiple signaling pathways by exclusively coupling to G(q/11) proteins. *J. Biol. Chem.* **275**: 9193-200 [PMID:10734055]
 38. Gründker C, Völker P, Griesinger F, Ramaswamy A, Nagy A, Schally AV and Emons G. (2002) Antitumor effects of the cytotoxic luteinizing hormone-releasing hormone analog AN-152 on human endometrial and ovarian cancers xenografted into nude mice. *Am. J. Obstet. Gynecol.* **187**: 528-37 [PMID:12237622]
 39. Halmos G and Schally AV. (2002) Changes in subcellular distribution of pituitary receptors for luteinizing hormone-releasing hormone (LH-RH) after treatment with the LH-RH antagonist cetorelix. *Proc. Natl. Acad. Sci. U.S.A.* **99**: 961-5 [PMID:11805337]
 40. Harrison GS, Wierman ME, Nett TM and Glode LM. (2004) Gonadotropin-releasing hormone and its receptor in normal and malignant cells. *Endocr. Relat. Cancer* **11**: 725-48 [PMID:15613448]
 41. Heding A, Vrecl M, Bogerd J, McGregor A, Sellar R, Taylor PL and Eidne KA. (1998) Gonadotropin-releasing hormone receptors with intracellular carboxyl-terminal tails undergo acute desensitization of total inositol phosphate production and exhibit accelerated internalization kinetics. *J. Biol. Chem.* **273**: 11472-7 [PMID:9565559]
 42. Heitman LH and Ijzerman AP. (2008) G protein-coupled receptors of the hypothalamic-pituitary-gonadal axis: a case for GnRH, LH, FSH, and GPR54 receptor ligands. *Med Res Rev* **28**: 975-1011 [PMID:18561294]
 43. Heitman LH, Ye K, Oosterom J and Ijzerman AP. (2008) Amiloride derivatives and a nonpeptidic antagonist bind at two distinct allosteric sites in the human gonadotropin-releasing hormone receptor. *Mol. Pharmacol.* **73**: 1808-15 [PMID:18344315]
 44. Herbst KL. (2003) Gonadotropin-releasing hormone antagonists. *Curr Opin Pharmacol* **3**: 660-6 [PMID:14644020]
 45. Hirdes W, Dinu C, Bauer CK, Boehm U and Schwarz JR. (2010) Gonadotropin-releasing hormone inhibits ether-à-go-go-related gene K⁺ currents in mouse gonadotropes. *Endocrinology* **151**: 1079-88 [PMID:20068004]
 46. Hoffmann SH, ter Laak T, Kühne R, Reiländer H and Beckers T. (2000) Residues within transmembrane helices 2 and 5 of the human gonadotropin-releasing hormone receptor contribute to agonist and antagonist binding. *Mol. Endocrinol.* **14**: 1099-115 [PMID:10894158]
 47. Huirne JA and Lambalk CB. (2001) Gonadotropin-releasing-hormone-receptor antagonists. *Lancet* **358**: 1793-803 [PMID:11734258]

48. Janovick JA, Maya-Nunez G and Conn PM. (2002) Rescue of hypogonadotropic hypogonadism-causing and manufactured GnRH receptor mutants by a specific protein-folding template: misrouted proteins as a novel disease etiology and therapeutic target. *J. Clin. Endocrinol. Metab.* **87**: 3255-62 [PMID:12107234]
49. Kaiser UB, Zhao D, Cardona GR and Chin WW. (1992) Isolation and characterization of cDNAs encoding the rat pituitary gonadotropin-releasing hormone receptor. *Biochem. Biophys. Res. Commun.* **189**: 1645-52 [PMID:1339279]
50. Kakar SS, Grizzle WE and Neill JD. (1994) The nucleotide sequences of human GnRH receptors in breast and ovarian tumors are identical with that found in pituitary. *Mol. Cell. Endocrinol.* **106**: 145-9 [PMID:7534732]
51. Kakar SS and Jennes L. (1995) Expression of gonadotropin-releasing hormone and gonadotropin-releasing hormone receptor mRNAs in various non-reproductive human tissues. *Cancer Lett.* **98**: 57-62 [PMID:8529206]
52. Kakar SS, Musgrove LC, Devor DC, Sellers JC and Neill JD. (1992) Cloning, sequencing, and expression of human gonadotropin releasing hormone (GnRH) receptor. *Biochem. Biophys. Res. Commun.* **189**: 289-95 [PMID:1333190]
53. Kiesel LA, Rody A, Greb RR and Szilágyi A. (2002) Clinical use of GnRH analogues. *Clin. Endocrinol. (Oxf)* **56**: 677-87 [PMID:12072036]
54. Kim SM, Yoo T, Lee SY, Kim EJ, Lee SM, Lee MH, Han MY, Jung SH, Choi JH and Ryu KH *et al.* (2015) Effect of SKI2670, a novel, orally active, non-peptide GnRH antagonist, on hypothalamic-pituitary-gonadal axis. *Life Sci.* **139**: 166-74 [PMID:26321528]
55. Kottler ML, Lorenzo F, Bergametti F, Commerçon P, Souchier C and Counis R. (1995) Subregional mapping of the human gonadotropin-releasing hormone receptor (GnRH-R) gene to 4q between the markers D4S392 and D4S409. *Hum. Genet.* **96**: 477-80 [PMID:7557974]
56. Kovacs M, Seprodi J, Koppan M, Horvath JE, Vincze B, Teplan I and Flerko B. (2002) Lamprey gonadotropin hormone-releasing hormone-III has no selective follicle-stimulating hormone-releasing effect in rats. *J. Neuroendocrinol.* **14**: 647-55 [PMID:12153467]
57. Kroeger KM, Hanyaloglu AC, Seeber RM, Miles LE and Eidne KA. (2001) Constitutive and agonist-dependent homo-oligomerization of the thyrotropin-releasing hormone receptor. Detection in living cells using bioluminescence resonance energy transfer. *J. Biol. Chem.* **276**: 12736-43 [PMID:11278883]
58. Krsmanovic LZ, Mores N, Navarro CE, Arora KK and Catt KJ. (2003) An agonist-induced switch in G protein coupling of the gonadotropin-releasing hormone receptor regulates pulsatile neuropeptide secretion. *Proc. Natl. Acad. Sci. U.S.A.* **100**: 2969-74 [PMID:12591945]
59. Kudo A, Park MK and Kawashima S. (1993) Isolation of rat GnRH receptor cDNA having different 5'-noncoding sequence. *Zool. Sci.* **10**: 863-7 [PMID:7764374]
60. Kuphal D, Janovick JA, Kaiser UB, Chin WW and Conn PM. (1994) Stable transfection of GH3 cells with rat gonadotropin-releasing hormone receptor complementary deoxyribonucleic acid results in expression of a receptor coupled to cyclic adenosine 3',5'-monophosphate-dependent prolactin release via a G-protein. *Endocrinology* **135**: 315-20 [PMID:8013367]
61. La Rosa S, Celato N, Uccella S and Capella C. (2000) Detection of gonadotropin-releasing hormone receptor in normal human pituitary cells and pituitary adenomas using immunohistochemistry. *Virchows Arch.* **437**: 264-9 [PMID:11037346]
62. Lau HL, Zhu XM, Leung PC, Chan LW, Chen GF, Chan PS, Yu KL and Chan FL. (2001) Detection of mRNA expression of gonadotropin-releasing hormone and its receptor in normal and neoplastic rat prostates. *Int. J. Oncol.* **19**: 1193-201 [PMID:11713589]
63. Leañós-Miranda A, Ulloa-Aguirre A, Ji TH, Janovick JA and Conn PM. (2003) Dominant-negative action of disease-causing gonadotropin-releasing hormone receptor (GnRHR) mutants: a trait that potentially coevolved with decreased plasma membrane expression of GnRHR in humans. *J. Clin. Endocrinol. Metab.* **88**: 3360-7 [PMID:12843188]
64. Lee CY, Ho J, Chow SN, Yasojima K, Schwab C and McGeer PL. (2000) Immunoidentification of gonadotropin releasing hormone receptor in human sperm, pituitary and cancer cells. *Am. J. Reprod.*

- Immunol.* **44**: 170-7 [PMID:11028904]
65. Leung PC, Squire J, Peng C, Fan N, Hayden MR and Olofsson JI. (1995) Mapping of the gonadotropin-releasing hormone (GnRH) receptor gene to human chromosome 4q21.2 by fluorescence in situ hybridization. *Mamm. Genome* **6**: 309-10 [PMID:7613048]
 66. Levi LN, Ben-Aroya N, Tel-Or S, Palmon A, Burstein Y and Koch Y. (1996) Expression of the gene for the receptor of gonadotropin-releasing hormone in the rat mammary gland. *FEBS Lett.* **379**: 186-90 [PMID:8635589]
 67. Limonta P, Moretti RM, Marelli MM and Motta M. (2003) The biology of gonadotropin hormone-releasing hormone: role in the control of tumor growth and progression in humans. *Front Neuroendocrinol* **24**: 279-95 [PMID:14726258]
 68. Liu SV, Liu S and Pinski J. (2011) Luteinizing hormone-releasing hormone receptor targeted agents for prostate cancer. *Expert Opin Investig Drugs* **20**: 769-78 [PMID:21449823]
 69. Lovas S, Pályi I, Vincze B, Horváth J, Kovács M, Mezö I, Tóth G, Teplán I and Murphy RF. (1998) Direct anticancer activity of gonadotropin-releasing hormone-III. *J. Pept. Res.* **52**: 384-9 [PMID:9894843]
 70. Lu ZL, Coetsee M, White CD and Millar RP. (2007) Structural determinants for ligand-receptor conformational selection in a peptide G protein-coupled receptor. *J. Biol. Chem.* **282**: 17921-9 [PMID:17452338]
 71. Maiti K, Li JH, Wang AF, Acharjee S, Kim WP, Im WB, Kwon HB and Seong JY. (2003) GnRH-II analogs for selective activation and inhibition of non-mammalian and type-II mammalian GnRH receptors. *Mol. Cells* **16**: 173-9 [PMID:14651258]
 72. Marian J and Conn PM. (1983) Subcellular localization of the receptor for gonadotropin-releasing hormone in pituitary and ovarian tissue. *Endocrinology* **112**: 104-112 [PMID:6291912]
 73. Mason AJ, Hayflick JS, Zoeller RT, Young 3rd WS, Phillips HS, Nikolics K and Seeburg PH. (1986) A deletion truncating the gonadotropin-releasing hormone gene is responsible for hypogonadism in the hpg mouse. *Science* **234**: 1366-71 [PMID:3024317]
 74. Maudsley S, Davidson L, Pawson AJ, Chan R, López de Maturana R and Millar RP. (2004) Gonadotropin-releasing hormone (GnRH) antagonists promote proapoptotic signaling in peripheral reproductive tumor cells by activating a G α coupling state of the type I GnRH receptor. *Cancer Res.* **64**: 7533-44 [PMID:15492280]
 75. Mezo G, Czajlik A, Manea M, Jakab A, Farkas V, Majer Z, Vass E, Bodor A, Kapuvári B and Boldizsár M *et al.*. (2007) Structure, enzymatic stability and antitumor activity of sea lamprey GnRH-III and its dimer derivatives. *Peptides* **28**: 806-20 [PMID:17254668]
 76. Millar R, Lowe S, Conklin D, Pawson A, Maudsley S, Troskie B, Ott T, Millar M, Lincoln G and Sellar RE *et al.*. (2001) A novel mammalian receptor for the evolutionarily conserved type II GnRH. *Proc. Natl. Acad. Sci. U.S.A.* **98**: 9636-41 [PMID:11493674]
 77. Millar RP. (2005) GnRHs and GnRH receptors. *Anim. Reprod. Sci.* **88**: 5-28 [PMID:16140177]
 78. Millar RP, Lu ZL, Pawson AJ, Flanagan CA, Morgan K and Maudsley SR. (2004) Gonadotropin-releasing hormone receptors. *Endocr. Rev.* **25**: 235-75 [PMID:15082521]
 79. Miller GM, Alexander JM and Klibanski A. (1996) Gonadotropin-releasing hormone messenger RNA expression in gonadotroph tumors and normal human pituitary. *J Clin Endocrinol Metab* **81**: 80-83 [PMID:8550798]
 80. Miwa K, Hitaka T, Imada T, Sasaki S, Yoshimatsu M, Kusaka M, Tanaka A, Nakata D, Furuya S and Endo S *et al.*. (2011) Discovery of 1-{4-[1-(2,6-difluorobenzyl)-5-[(dimethylamino)methyl]-3-(6-methoxy-pyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-6-yl]phenyl}-3-methoxyurea (TAK-385) as a potent, orally active, non-peptide antagonist of the human gonadotropin-releasing hormone receptor. *J. Med. Chem.* **54**: 4998-5012 [PMID:21657270]
 81. Morgan K, Conklin D, Pawson AJ, Sellar R, Ott TR and Millar RP. (2003) A transcriptionally active human type II gonadotropin-releasing hormone receptor gene homolog overlaps two genes in the antisense orientation on chromosome 1q.12. *Endocrinology* **144**: 423-36 [PMID:12538601]
 82. Morrison N, Sellar RE, Boyd E, Eidne KA and Connor JM. (1994) Assignment of the gene encoding the

- human gonadotropin-releasing hormone receptor to 4q13.2-13.3 by fluorescence in situ hybridization. *Hum. Genet.* **93**: 714-5 [PMID:8005601]
83. Naor Z, Clayton RN and Catt KJ. (1980) Characterization of gonadotropin-releasing hormone receptors in cultured rat pituitary cells. *Endocrinology* **107**: 1144-52 [PMID:6250793]
 84. Nederpelt I, Georgi V, Schiele F, Nowak-Reppel K, Fernández-Montalván AE, IJzerman AP and Heitman LH. (2016) Characterization of 12 GnRH peptide agonists - a kinetic perspective. *Br. J. Pharmacol.* **173**: 128-41 [PMID:26398856]
 85. Nederpelt I, Vergroesen RD, IJzerman AP and Heitman LH. (2016) Persistent GnRH receptor activation in pituitary α T3-1 cells analyzed with a label-free technology. *Biosens Bioelectron* **79**: 721-7 [PMID:26774084]
 86. Neill JD. (2002) GnRH and GnRH receptor genes in the human genome. *Endocrinology* **143**: 737-43 [PMID:11861490]
 87. Netiv E, Liscovitch M and Naor Z. (1991) Delayed activation of phospholipase D by gonadotropin-releasing hormone in a clonal pituitary gonadotrope cell line (alpha T3-1). *FEBS Lett.* **295**: 107-9 [PMID:1765140]
 88. Olberg DE, Bauer N, Andressen KW, Hjørnevik T, Cumming P, Levy FO, Klaveness J, Haraldsen I and Sutcliffe JL. (2016) Brain penetrant small molecule (18)F-GnRH receptor (GnRH-R) antagonists: Synthesis and preliminary positron emission tomography imaging in rats. *Nucl. Med. Biol.* **43**: 478-89 [PMID:27236283]
 89. Papanikolaou EG, Kolibianakis E and Devroey P. (2005) Emerging drugs in assisted reproduction. *Expert Opin Emerg Drugs* **10**: 425-40 [PMID:15934877]
 90. Pask AJ, Kanasaki H, Kaiser UB, Conn PM, Janovick JA, Stockton DW, Hess DL, Justice MJ and Behringer RR. (2005) A novel mouse model of hypogonadotropic hypogonadism: N-ethyl-N-nitrosourea-induced gonadotropin-releasing hormone receptor gene mutation. *Mol. Endocrinol.* **19**: 972-81 [PMID:15625238]
 91. Pelletier JC, Chengalvala M, Cottom J, Feingold I, Garrick L, Green D, Hauze D, Huselton C, Jetter J and Kao W *et al.*. (2008) 2-phenyl-4-piperazinylbenzimidazoles: orally active inhibitors of the gonadotropin releasing hormone (GnRH) receptor. *Bioorg. Med. Chem.* **16**: 6617-40 [PMID:18511284]
 92. Pelletier JC, Chengalvala MV, Cottom JE, Feingold IB, Green DM, Hauze DB, Huselton CA, Jetter JW, Kopf GS and Lundquist JT *et al.*. (2009) Discovery of 6-((4-[2-(4-tert-butylphenyl)-1H-benzimidazol-4-yl]piperazin-1-yl)methyl)quinoxaline (WAY-207024): an orally active antagonist of the gonadotropin releasing hormone receptor (GnRH-R). *J. Med. Chem.* **52**: 2148-52 [PMID:19271735]
 93. Peng C, Fan NC, Ligier M, Väänänen J and Leung PC. (1994) Expression and regulation of gonadotropin-releasing hormone (GnRH) and GnRH receptor messenger ribonucleic acids in human granulosa-luteal cells. *Endocrinology* **135**: 1740-6 [PMID:7956897]
 94. Perrin MH, Bilezikjian LM, Hoeger C, Donaldson CJ, Rivier J, Haas Y and Vale WW. (1993) Molecular and functional characterization of GnRH receptors cloned from rat pituitary and a mouse pituitary tumor cell line. *Biochem. Biophys. Res. Commun.* **191**: 1139-44 [PMID:7916600]
 95. Perrin MH, Haas Y, Rivier JE and Vale WW. (1983) Gonadotropin-releasing hormone binding to rat anterior pituitary membrane homogenates. Comparison of antagonists and agonists using radiolabeled antagonist and agonist. *Mol. Pharmacol.* **23**: 44-51 [PMID:6346049]
 96. Poulin B, Rich N, Mitev Y, Gautron JP, Kordon C, Enjalbert A and Drouva SV. (1996) Differential involvement of calcium channels and protein kinase-C activity in GnRH-induced phospholipase-C, -A2 and -D activation in a gonadotrope cell line (alpha T3-1). *Mol. Cell. Endocrinol.* **122**: 33-50 [PMID:8898346]
 97. Reeves JJ, Séguin C, Lefebvre FA, Kelly PA and Labrie F. (1980) Similar luteinizing hormone-releasing hormone binding sites in rat anterior pituitary and ovary. *Proc. Natl. Acad. Sci. U.S.A.* **77**: 5567-71 [PMID:6254091]
 98. Reinhart J, Mertz LM and Catt KJ. (1992) Molecular cloning and expression of cDNA encoding the murine gonadotropin-releasing hormone receptor. *J. Biol. Chem.* **267**: 21281-4 [PMID:1328228]
 99. Rivier J, Theobald P, Porter J, Perrin M, Gunnet J, Hahn DW and Rivier C. (1991) Gonadotropin releasing hormone antagonists: novel structures incorporating N omega-cyano modified guanidine moieties.

- Biochem. Biophys. Res. Commun.* **176**: 406-12 [PMID:1850267]
100. Saleh-Abady MM, Naderi-Manesh H, Alizadeh A, Shamsipour F, Balalaie S and Arabanian A. (2010) Anticancer activity of a new gonadotropin releasing hormone analogue. *Biopolymers* **94**: 292-7 [PMID:19908246]
 101. Sanno N, Jin L, Qian X, Osamura RY, Scheithauer BW, Kovacs K and Lloyd RV. (1997) Gonadotropin-releasing hormone and gonadotropin-releasing hormone receptor messenger ribonucleic acids expression in nontumorous and neoplastic pituitaries. *J Clin Endocrinol Metab* **82**: 1974-1982 [PMID:9177416]
 102. Sasaki S, Cho N, Nara Y, Harada M, Endo S, Suzuki N, Furuya S and Fujino M. (2003) Discovery of a thieno[2,3-d]pyrimidine-2,4-dione bearing a p-methoxyureidophenyl moiety at the 6-position: a highly potent and orally bioavailable non-peptide antagonist for the human luteinizing hormone-releasing hormone receptor. *J. Med. Chem.* **46**: 113-24 [PMID:12502365]
 103. Schally AV, Arimura A, Kastin AJ, Matsuo H, Baba Y, Redding TW, Nair RM, Debeljuk L and White WF. (1971) Gonadotropin-releasing hormone: one polypeptide regulates secretion of luteinizing and follicle-stimulating hormones. *Science* **173**: 1036-8 [PMID:4938639]
 104. Schally AV, Engel JB, Emons G, Block NL and Pinski J. (2011) Use of analogs of peptide hormones conjugated to cytotoxic radicals for chemotherapy targeted to receptors on tumors. *Curr Drug Deliv* **8**: 11-25 [PMID:21034424]
 105. Schally AV and Nagy A. (2004) Chemotherapy targeted to cancers through tumoral hormone receptors. *Trends Endocrinol. Metab.* **15**: 300-10 [PMID:15350601]
 106. Shah BH and Milligan G. (1994) The gonadotrophin-releasing hormone receptor of alpha T3-1 pituitary cells regulates cellular levels of both of the phosphoinositidase C-linked G proteins, Gq alpha and G11 alpha, equally. *Mol. Pharmacol.* **46**: 1-7 [PMID:8058044]
 107. Silver MR, Nucci NV, Root AR, Reed KL and Sower SA. (2005) Cloning and characterization of a functional type II gonadotropin-releasing hormone receptor with a lengthy carboxy-terminal tail from an ancestral vertebrate, the sea lamprey. *Endocrinology* **146**: 3351-61 [PMID:15878963]
 108. Stewart AJ, Sellar R, Wilson DJ, Millar RP and Lu ZL. (2008) Identification of a novel ligand binding residue Arg38(1.35) in the human gonadotropin-releasing hormone receptor. *Mol. Pharmacol.* **73**: 75-81 [PMID:17942747]
 109. Struthers RS, Xie Q, Sullivan SK, Reinhart GJ, Kohout TA, Zhu YF, Chen C, Liu XJ, Ling N and Yang W *et al.* (2007) Pharmacological characterization of a novel nonpeptide antagonist of the human gonadotropin-releasing hormone receptor, NBI-42902. *Endocrinology* **148**: 857-67 [PMID:17095587]
 110. Sullivan SK, Brown MS, Gao Y, Loweth CJ, Lio FM, Crowe PD, Struthers RS and Betz SF. (2006) Allosteric and orthosteric binding modes of two nonpeptide human gonadotropin-releasing hormone receptor antagonists. *Biochemistry* **45**: 15327-37 [PMID:17176055]
 111. Sullivan SK, Hoare SR, Fleck BA, Zhu YF, Heise CE, Struthers RS and Crowe PD. (2006) Kinetics of nonpeptide antagonist binding to the human gonadotropin-releasing hormone receptor: Implications for structure-activity relationships and insurmountable antagonism. *Biochem. Pharmacol.* **72**: 838-49 [PMID:16930559]
 112. Tan O and Bukulmez O. (2011) Biochemistry, molecular biology and cell biology of gonadotropin-releasing hormone antagonists. *Curr. Opin. Obstet. Gynecol.* **23**: 238-44 [PMID:21666463]
 113. Themmen APN and Huhtaniemi IT. (2000) Mutations of gonadotropins and gonadotropin receptors: elucidating the physiology and pathophysiology of pituitary-gonadal function. *Endocr. Rev.* **21**: 551-83 [PMID:11041448]
 114. Tsui KH, Lee WL, Seow KM, Yang LW, Wang SY, Wang PH, Chang CL, Yen MS, Cheng JT and Chen CP. (2014) Effect of gonadotropin-releasing hormone agonist on ES-2 ovarian cancer cells. *Taiwan J Obstet Gynecol* **53**: 35-42 [PMID:24767644]
 115. Tsutsumi M, Zhou W, Millar RP, Mellon PL, Roberts JL, Flanagan CA, Dong K, Gillo B and Sealfon SC. (1992) Cloning and functional expression of a mouse gonadotropin-releasing hormone receptor. *Mol. Endocrinol.* **6**: 1163-9 [PMID:1324422]
 116. Tsutsumi R, Mistry D and Webster NJ. (2010) Signaling responses to pulsatile gonadotropin-releasing

- hormone in LbetaT2 gonadotrope cells. *J. Biol. Chem.* **285**: 20262-72 [PMID:20406815]
117. Tucci FC, Zhu YF, Struthers RS, Guo Z, Gross TD, Rowbottom MW, Acevedo O, Gao Y, Saunders J and Xie Q *et al.*. (2005) 3-[(2R)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-5-(2-fluoro-3-methoxyphenyl)-6-methylpyrimidin-2,4-dione (NBI 42902) as a potent and orally active antagonist of the human gonadotropin-releasing hormone receptor. Design, synthesis, and in vitro and in vivo characterization. *J. Med. Chem.* **48**: 1169-78 [PMID:15715483]
 118. Van Poppel H. (2010) Evaluation of degarelix in the management of prostate cancer. *Cancer Manag Res* **2**: 39-52 [PMID:21188095]
 119. Wang C, Ma Y, Feng S, Liu K and Zhou N. (2015) Gonadotropin-releasing hormone receptor-targeted paclitaxel-degarelix conjugate: synthesis and in vitro evaluation. *J. Pept. Sci.* **21**: 569-76 [PMID:25851250]
 120. Weckermann D and Harzmann R. (2004) Hormone therapy in prostate cancer: LHRH antagonists versus LHRH analogues. *Eur. Urol.* **46**: 279-83; discussion 283-4 [PMID:15306097]
 121. White RB, Eisen JA, Kasten TL and Fernald RD. (1998) Second gene for gonadotropin-releasing hormone in humans. *Proc. Natl. Acad. Sci. U.S.A.* **95**: 305-9 [PMID:9419371]
 122. Williams BL, Akazome Y, Oka Y and Eisthen HL. (2014) Dynamic evolution of the GnRH receptor gene family in vertebrates. *BMC Evol. Biol.* **14**: 215 [PMID:25344287]
 123. Wu HM, Wang HS, Huang HY, Lai CH, Lee CL, Soong YK and Leung PC. (2013) Gonadotropin-releasing hormone type II (GnRH-II) agonist regulates the invasiveness of endometrial cancer cells through the GnRH-I receptor and mitogen-activated protein kinase (MAPK)-dependent activation of matrix metalloproteinase (MMP)-2. *BMC Cancer* **13**: 300 [PMID:23786715]
 124. Yahalom D, Chen A, Ben-Aroya N, Rahimpour S, Kaganovsky E, Okon E, Fridkin M and Koch Y. (1999) The gonadotropin-releasing hormone family of neuropeptides in the brain of human, bovine and rat: identification of a third isoform. *FEBS Lett.* **463**: 289-94 [PMID:10606740]