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From *KISS1* to Kisspeptins: An Historical Perspective and Suggested Nomenclature

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Abstract

The cancer suppressor gene, *KISS1*, was initially described as having an important role in inhibiting cancer metastasis. Since then, KISS1 and its receptor, KISS1R, have been shown to play a key role in controlling the onset of puberty of reproductive physiology in the human and other species. Recent studies have also linked *KISS1/KISS1R*/kisspeptin to other processes, such as vasoconstriction, aging, adipocyte physiology, and perhaps as a molecular conduit linking metabolism and reproduction. This article highlights the history of *KISS1/KISS1R*/kisspeptin biology and proposes a consensus for nomenclature of the key molecules in this signaling pathway.

Keywords

KISS1; Kisspeptin; Kisspeptin receptor; metastin

1.0 Introduction

The cancer suppressor gene, *KISS1*, may have been named with a bit of whimsy, to ensure everyone knew (or might guess) where it was discovered— in Hershey, Pennsylvania, of course, the home of the famous Hershey Kisses (26,27)! However, the impact of the discovery of the *KISS1* gene now reaches far beyond the chocolate morsel. The *KISS1* gene encodes for a hydrophobic 145 amino acid protein (1,24,40), which can be cleaved into a 54 amino acid protein, originally called metastin for its ability to inhibit cancer metastasis (40). Both the 145 and 54 amino acid proteins contain a sequence that predisposes the proteins for ubiquitination and proteosome degradation, suggesting that they may have a short half-life (14). The 54 amino acid metastin and the shorter peptides (10, 13 and 14 amino acids long) were collectively named kisspeptins, because they are the proteolytic bi-products of a common precursor protein encoded by the *KISS1* gene (24). It is unclear how the shorter peptides are processed from the larger peptide or whether the shorter peptides are bio-available (40). Nevertheless, when isolated, each of these peptides has a common C-terminal amidation site that leads to strong binding with their receptor (6,25,36,40,58). The larger peptide comprises some variability

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among species, whereas the 10 amino acid C-terminus peptide is well conserved and binds to and activates KISS1R (24,26,36,40). *KISS1* and *KISS1R* genes are both expressed in various tissues, including the placenta, brain, pituitary, gonads, liver, pancreas, intestines, aorta, coronary artery and umbilical vein (26,34,36,40,45).

2.0 Discovery

KISS1 was discovered in 1996 (26). The gene coding for the kisspeptin receptor, *KISS1R*, which shares a modest sequence identity with the gene coding for galanin receptor 2, was described in 1999 (25); however, it was not until 2003 that the receptor caught the attention of reproductive physiologists. Scientists became familiar with KISS1R when it was known simply as the orphan G protein-coupled receptor (GPR) 54 or as code name “Harry Potter” by investigators at Paradigm Therapeutics, who were the first to disrupt its expression in mice (49).

In 2003, reports by two independent groups brought kisspeptin-KISS1R signaling to the immediate and rapt attention of reproductive biologists. Within months of one another, Nicolas De Roux and his colleagues and Stephanie Seminara and her collaborators described the genetic basis of the hypothalamic hypogonadism found in some of their patients who failed to show normal sexual maturation. Their genetic analysis revealed that mutations in *KISS1R* were associated with impaired pubertal maturation (8,49). This mutation was initially described in several consanguineous families, and a few other non-related patients; and later, the phenotype was recapitulated in mice that have deletional mutations of *Kiss1r*, lending credence to the argument that this was indeed the causal agent (11,49). The discovery of a single receptor gene mutation that has profound effects upon the activation of pubertal maturation without other discernable effects (10,11,49) kindled enthusiasm to revisit an old unresolved problem— how the hypothalamic-pituitary-gonadal axis is activated at the time of puberty. Fanning this excitement were two other important corroborating discoveries— first, mice with deletional mutations in *Kiss1* itself (coding for the *Kiss1r* ligand) fail to undergo normal pubertal maturation and second, humans with an “activating” mutation of *KISS1R* develop precocious puberty (7,59).

3.0 Role of Kisspeptin and KISS1 Receptor

Since the discovery of *KISS1* and *KISS1R*, numerous reports about kisspeptin signaling have appeared, including some that extend well beyond the realm of cancer biology and the physiology of puberty. These findings have been recently reviewed by Mead (33), Seminara (51) and Popa (43), and several of these topics will be discussed in further detail in this issue of *Peptides* and thus mentioned only briefly here.

The *KISS1* gene was originally found to inhibit metastasis of cancer cells (26,27) and later discovered to be expressed abundantly in the placenta (1). Since then, it has been shown that *KISS1* gene expression down-regulates the activity of matrix metalloproteinases (1,16,62), which is thought to be the mechanism that *KISS1* suppresses cancer metastasis and may also have a role in placentation and perhaps the pathogenesis of preeclampsia (1,19).

In the brain of rodents, *Kiss1* is located in the anteroventral periventricular nucleus (AVPV), arcuate nucleus (Arc), anterodorsal preoptic nucleus (ADP), amygdala, and bed nucleus of the stria terminalis (BnST) (12,38,55), and Kiss1 (or the kisspeptin protein) has been identified in homologous areas in fish (21), sheep (35) and monkeys (52). Furthermore, the majority of GnRH neurons express the kisspeptin receptor, *Kiss1r* (18,35,41). Miniscule molar amounts of kisspeptin (in the femptomole range) can induce robust GnRH/LH secretion in a wide range of species, including rodents, primates, cattle and fish (9,12,18,20,29,32,35,37,52,60), and kisspeptins can directly (and perhaps indirectly) stimulate GnRH neurons (13,42). Levels of

Kiss1 mRNA increase in the AVPV in association with the onset of puberty (13), and GnRH neurons become more sensitive to the effects of kisspeptin, which may reflect an increase in the number of *Kiss1*/GnRH appositions (5,13) or an undefined "maturation" of the Kiss1r that gates signal transduction (13). Finally, the administration of kisspeptins can stimulate GnRH/LH secretion in prepubertal primates and even advance pubertal onset in some species (20, 29,37,50).

Gonadal sex steroids differentially regulate *Kiss1* mRNA expression in AVPV and Arc of the hypothalamus (38,55,56) and induce *Kiss1* expression in pituitary gonadotropes (45), likely via the estrogen receptor (ER) alpha (45,55). However, recent reports suggest that in the hypothalamus, ER beta and the progesterone receptor may also influence whether the effect of estradiol on *Kiss1* expression is stimulatory or inhibitory (47). The expression of *Kiss1* in the AVPV of the rodent is sexually differentiated, with females showing greater expression than males (5,22). Similar results have been demonstrated in some species of fish, but in at least one reported instance, males have greater *Kiss1* expression than females (21). In female rodents, the sexually dimorphic pattern of *Kiss1* expression can be reversed by exposure to androgens during the perinatal critical period (22). Kisspeptin-Kiss1r signaling seems to be critical for the preovulatory LH surge with *Kiss1* mRNA expression being highest prior to the LH surge in the AVPV (57) [and the ovary as well (3)]. Moreover, antiserum to kisspeptin can block the LH surge in the rat, arguing for the importance of kisspeptin signaling for generating the preovulatory GnRH/LH surge (23). Despite this inference, it would appear that kisspeptin-GnRH signaling is not the entire story, since mice that are null for *Kiss1r* retain the ability to show a GnRH/LH surge in response to an estradiol challenge (10). Redundant pathways may compensate in the absence of *Kiss1r* (when gonadal sex steroids are replaced) or perhaps compensatory mechanisms develop to "correct" the genetic lesion (10). The expression of *Kiss1* mRNA is down-regulated in both the ARC and AVPV during lactation (61), and *Kiss1* expression is seasonally regulated in some mammals (31,44) and fish (21).

Additionally, *Kiss1* mRNA is expressed in the alpha and beta cells of the cells of pancreatic Islets of Langerhan (15). Although the effect of kisspeptins upon glucose mediated insulin secretion in normal animals is equivocal, in diabetic rats, kisspeptin can apparently rescue gonadotropin secretion (4,15,53). *Kiss1* mRNA in the Arc is also decreased in leptin-deficient male mice and can be partially restored with leptin treatment (56). In addition, injections of kisspeptin have been shown to stimulate gonadotropin secretion in rodents treated with leptin antibodies (4), suggesting that kisspeptin may be involved in leptin signaling in the neuroendocrine reproductive axis. Ghrelin has been shown to have a countervailing effect on the ability of kisspeptin to regulate reproductive function (30). Another recent report has shown that kisspeptin signaling can affect vasoconstriction (34), and *Kiss1* mRNA expression is regulated in adipose tissue (2), which suggests that kisspeptin could serve as a molecular link between metabolism and reproduction.

4.0 Nomenclature

With the broad interest in kisspeptin-KISS1R signaling, it is important to develop more consistency in nomenclature of the key molecules. Several terms that refer to kisspeptin and kisspeptin receptor have been used over the past 5 years. For example, in reference to just the receptor, one can find AXOR12, hOT7T175, GPR54, KISS1R, KiSS1 and the metastin receptor (24,25,36,40,46). Further confusion results when distinguishing among the gene, the mRNA, and the protein, and when differentiating among species.

The kisspeptin protein was originally named metastin (specifically referring to one of the peptide products of the gene); however, the term 'kisspeptin' has come into more widespread and general use. We recommend that 'kisspeptin' be used in reference to the protein product

(s) of the gene, because the physiological significance of the protein extends far beyond its role as “suppressor” of metastasis. We also suggest that metastin be used only in references to human kisspeptin-54, as this is where it was discovered and there are considerable sequence differences between the human 54 amino acid peptide and Kp-54 from other species (24,26, 36,40). Furthermore, the use of the term metastin should be limited to cancer biology, where its name has direct relevance.

The Human Genome Organization Gene Nomenclature Committee (HGNC) has proposed the use of *KISS1* as the symbol for the kisspeptin gene (http://www.genenames.org/data/hgnc_data.php?hgnc_id=6341). With respect to other species, the international committees that were established to standardize the nomenclature for the mouse and rat genomes recommend that when possible, the same symbol be used for orthologs among human, mouse and rat, except that the symbol should begin with an upper case letter, followed by all lowercase letters / numbers (http://www.informatics.jax.org/mgihome/nomen/gene.shtml). In addition, they recommend that gene symbols be italicized. Based on these recommendations, we suggest that *KISS1* be used to represent the human kisspeptin gene and *Kiss1* to represent non-human kisspeptin genes. [The use of hyphenation (Kiss-1) is expressly discouraged because various search engines handle the hyphen differently and this can significantly affect search outcomes.] Furthermore, we suggest that non-italicized versions of the gene nomenclature be used to refer to the protein products of *KISS1* (KISS1 for human and Kiss1 for other species)—but spelling out ‘kisspeptin’ would always appropriate, and is an easy way to denote both the protein product of *KISS1* and its various peptide products collectively.

Distinguishing between the peptide products that are cleaved from the 145 amino acid protein requires clarity. Some reports have made reference to the peptide products as kisspeptin −54, -14, -13, and -10, differentiating by peptide length (54 amino acids, 14 amino acids etc.). Others refer to the numerical sequence of amino acids that are cleaved from the original 145 amino acid pre-protein; for example, kisspeptin (68-121) or kisspeptin (112-121) refers to amino acids 68-121 or 112-121 of the original 145 amino acid peptide, which would also represent Kp-54 or Kp-10. Furthermore, others have made reference to kisspeptin-1 (68-121), which was likely done just in case another *KISS* gene were to be discovered. However, this nomenclature is infrequently used, and certainly a new system could be established if another *KISS* gene were discovered.

We know that each of the kisspeptin fragments is the proteolytic product of the common precursor and contains the all important C-terminal amide sequence. Since most reports distinguish between bioactive kisspeptin fragments based on size, it seems sensible to refer to their size, and abbreviate kisspeptin as KP or Kp. Thus, the abbreviation for the 10-amino acid kisspeptin peptide would be KP-10 for the human and Kp-10 for other species. A collection of various usages of *KISS1/KISS1R* and kisspeptins as well as our suggestions for simplified use is summarized in Tables 1 and 2.

In databases such as mouse genome informatics (MGI), *GPR54* was noted as the official name for the kisspeptin receptor from August 2001 until February 2006, after which the term *Kiss1r* was assigned, because the once orphaned receptor was no longer without a ligand. Likewise, HGNC recommends the use of *KISS1R* for the human kisspeptin receptor gene. If we follow those recommendations, the nonhuman *Gpr54* gene or mRNA should be referred to as *Kiss1r*, and the human gene or mRNA as *KISS1R* (again a matter of case to distinguish between the two). The same convention should then be applied to the receptor protein references -- Kiss1r should be used for the nonhuman receptor protein and KISS1R for the human receptor protein. It should be noted that the International Union of Pharmacology (IUPHAR) does not include an ‘R’ in receptor protein abbreviations and refers to kisspeptin

receptor protein as KiSS1. We believe there are good reasons for *not* following the IUPHAR convention in this case. First, using a lower/upper case 'i' as the only means to differentiate between the ligand and the receptor will cause considerable confusion. Second, most prior reports have used KiSS1 to refer to the *KISS1* gene product (i.e. the ligand, not the receptor), thus adding to the confusion. Third, there is no consistent way to distinguish the human from the nonhuman form of the peptide, since both would have to be KiSS1. We therefore argue that keeping the 'R' in KISS1R protein references allows for greater ease in distinguishing the peptide from its receptor and makes its designation consistent with that of its gene (*KISS1R)*.

5.0 Summary

The discovery of the *KISS1* and *KISS1R* genes has revealed a number of exciting discoveries in cancer biology and reproductive endocrinology. Recent studies have implicated these genes in aging and menopause (48), adipocyte physiology (2), as a molecular link between metabolism and reproduction (17), and perhaps as a target for the action of environmental estrogens on reproduction (39). This issue of *Peptides* will serve as collection of these critical new findings and perhaps serve as a springboard for ideas and collaborative efforts in the future. Who knew that a little KISS from Hershey PA would leave such lingering sweetness?

References

1. Bilban M, Ghaffari-Tabrizi N, Hintermann E, Bauer S, Molzer S, Zoratti C, Malli R, Sharabi A, Hiden U, Graier W, Knofler M, Andreae F, Wagner O, Quaranta V, Desoye G. Kisspeptin-10, a KiSS-1/metastin-derived decapeptide, is a physiological invasion inhibitor of primary human trophoblasts. J Cell Sci 2004;117:1319–1328. [PubMed: 15020672]
2. Brown RE, Imran SA, Ur E, Wilkinson M. KiSS-1 mRNA in adipose tissue is regulated by sex hormones and food intake. Mol Cell Endocrinol 2008;281:64–72. [PubMed: 18069123]
3. Castellano JM, Gaytan M, Roa J, Vigo E, Navarro VM, Bellido C, Dieguez C, Aguilar E, Sanchez-Criado JE, Pellicer A, Pinilla L, Gaytan F, Tena-Sempere M. Expression of KiSS-1 in rat ovary: putative local regulator of ovulation? Endocrinology 2006;147:4852–4862. [PubMed: 16825322]
4. Castellano JM, Navarro VM, Fernandez-Fernandez R, Roa J, Vigo E, Pineda R, Dieguez C, Aguilar E, Pinilla L, Tena-Sempere M. Expression of hypothalamic KiSS-1 system and rescue of defective gonadotropic responses by kisspeptin in streptozotocin-induced diabetic male rats. Diabetes 2006;55:2602–2610. [PubMed: 16936210]
5. Clarkson J, Herbison AE. Postnatal development of kisspeptin neurons in mouse hypothalamus; sexual dimorphism and projections to gonadotropin-releasing hormone neurons. Endocrinology 2006;147:5817–5825. [PubMed: 16959837]
6. Clements MK, McDonald TP, Wang R, Xie G, O'Dowd BF, George SR, Austin CP, Liu Q. FMRFamide-related neuropeptides are agonists of the orphan G-protein-coupled receptor GPR54. Biochem Biophys Res Commun 2001;284:1189–1193. [PubMed: 11414709]
7. d'Anglemont de Tassigny X, Fagg LA, Dixon JP, Day K, Leitch HG, Hendrick AG, Zahn D, Franceschini I, Caraty A, Carlton MB, Aparicio SA, Colledge WH. Hypogonadotropic hypogonadism in mice lacking a functional Kiss1 gene. Proc Natl Acad Sci U S A 2007;104:10714–10719. [PubMed: 17563351]
8. de Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proc Natl Acad Sci U S A 2003;100:10972–10976. [PubMed: 12944565]
9. Dhillo WS, Chaudhri OB, Patterson M, Thompson EL, Murphy KG, Badman MK, McGowan BM, Amber V, Patel S, Ghatei MA, Bloom SR. Kisspeptin-54 stimulates the hypothalamic-pituitary gonadal axis in human males. J Clin Endocrinol Metab 2005;90:6609–6615. [PubMed: 16174713]
10. Dungan HM, Gottsch ML, Zeng H, Gragerov A, Bergmann JE, Vassilatis DK, Clifton DK, Steiner RA. The role of kisspeptin-GPR54 signaling in the tonic regulation and surge release of gonadotropin-releasing hormone/luteinizing hormone. J Neurosci 2007;27:12088–12095. [PubMed: 17978050]

11. Funes S, Hedrick JA, Vassileva G, Markowitz L, Abbondanzo S, Golovko A, Yang S, Monsma FJ, Gustafson EL. The KiSS-1 receptor GPR54 is essential for the development of the murine reproductive system. Biochem Biophys Res Commun 2003;312:1357–1363. [PubMed: 14652023]
12. Gottsch ML, Cunningham MJ, Smith JT, Popa SM, Acohido BV, Crowley WF, Seminara S, Clifton DK, Steiner RA. A role for kisspeptins in the regulation of gonadotropin secretion in the mouse. Endocrinology 2004;145:4073–4077. [PubMed: 15217982]
13. Han SK, Gottsch ML, Lee KJ, Popa SM, Smith JT, Jakawich SK, Clifton DK, Steiner RA, Herbison AE. Activation of gonadotropin-releasing hormone neurons by kisspeptin as a neuroendocrine switch for the onset of puberty. J Neurosci 2005;25:11349–11356. [PubMed: 16339030]
14. Harms JF, Welch DR, Miele ME. KISS1 metastasis suppression and emergent pathways. Clin Exp Metastasis 2003;20:11–18. [PubMed: 12650602]
15. Hauge-Evans AC, Richardson CC, Milne HM, Christie MR, Persaud SJ, Jones PM. A role for kisspeptin in islet function. Diabetologia 2006;49:2131–2135. [PubMed: 16826407]
16. Hesling C, D'Incan M, Mansard S, Franck F, Corbin-Duval A, Chevenet C, Dechelotte P, Madelmont JC, Veyre A, Souteyrand P, Bignon YJ. In vivo and in situ modulation of the expression of genes involved in metastasis and angiogenesis in a patient treated with topical imiquimod for melanoma skin metastases. Br J Dermatol 2004;150:761–767. [PubMed: 15099376]
17. Hill J, Elmquist JK, Elias CF. Hypothalamic Pathways Linking Energy Balance and Reproduction. Am J Physiol Endocrinol Metab. 2008
18. Irwig MS, Fraley GS, Smith JT, Acohido BV, Popa SM, Cunningham MJ, Gottsch ML, Clifton DK, Steiner RA. Kisspeptin activation of gonadotropin releasing hormone neurons and regulation of KiSS-1 mRNA in the male rat. Neuroendocrinology 2004;80:264–272. [PubMed: 15665556]
19. Janneau JL, Maldonado-Estrada J, Tachdjian G, Miran I, Motte N, Saulnier P, Sabourin JC, Cote JF, Simon B, Frydman R, Chaouat G, Bellet D. Transcriptional expression of genes involved in cell invasion and migration by normal and tumoral trophoblast cells. J Clin Endocrinol Metab 2002;87:5336–5339. [PubMed: 12414911]
20. Kadokawa H, Matsui M, Hayashi K, Matsunaga N, Kawashima C, Shimizu T, Kida K, Miyamoto A. Peripheral administration of kisspeptin-10 increases plasma concentrations of GH as well as LH in prepubertal Holstein heifers. J Endocrinol 2008;196:331–334. [PubMed: 18252956]
21. Kanda S, Akazome Y, Matsunaga T, Yamamoto N, Yamada S, Tsukamura H, Maeda KI, Oka Y. Identification of KiSS-1 Product Kisspeptin and Steroid-Sensitive Sexually-Dimorphic Kisspeptin neurons in Medaka (Oryzias latipes). Endocrinology. 2008
22. Kauffman AS, Gottsch ML, Roa J, Byquist AC, Crown A, Clifton DK, Hoffman GE, Steiner RA, Tena-Sempere M. Sexual differentiation of Kiss1 gene expression in the brain of the rat. Endocrinology 2007;148:1774–1783. [PubMed: 17204549]
23. Kinoshita M, Tsukamura H, Adachi S, Matsui H, Uenoyama Y, Iwata K, Yamada S, Inoue K, Ohtaki T, Matsumoto H, Maeda K. Involvement of central metastin in the regulation of preovulatory luteinizing hormone surge and estrous cyclicity in female rats. Endocrinology 2005;146:4431–4436. [PubMed: 15976058]
24. Kotani M, Detheux M, Vandenbogaerde A, Communi D, Vanderwinden JM, Le Poul E, Brezillon S, Tyldesley R, Suarez-Huerta N, Vandeput F, Blanpain C, Schiffmann SN, Vassart G, Parmentier M. The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. J Biol Chem 2001;276:34631–34636. [PubMed: 11457843]
25. Lee DK, Nguyen T, O'Neill GP, Cheng R, Liu Y, Howard AD, Coulombe N, Tan CP, Tang-Nguyen AT, George SR, O'Dowd BF. Discovery of a receptor related to the galanin receptors. FEBS Lett 1999;446:103–107. [PubMed: 10100623]
26. Lee JH, Miele ME, Hicks DJ, Phillips KK, Trent JM, Weissman BE, Welch DR. KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. J Natl Cancer Inst 1996;88:1731–1737. [PubMed: 8944003]
27. Lee JH, Welch DR. Identification of highly expressed genes in metastasis-suppressed chromosome 6/human malignant melanoma hybrid cells using subtractive hybridization and differential display. Int J Cancer 1997;71:1035–1044. [PubMed: 9185708]

28. Lee JH, Welch DR. Suppression of metastasis in human breast carcinoma MDA-MB-435 cells after transfection with the metastasis suppressor gene, KiSS-1. Cancer Res 1997;57:2384–2387. [PubMed: 9192814]
29. Lents C, Heidorn N, Barb C, Ford J. Central and peripheral administration of kisspeptin activates gonadotropin but not somatotropin secretion in prepubertal gilts. Reproduction. 2008
30. Martini AC, Fernandez-Fernandez R, Tovar S, Navarro VM, Vigo E, Vazquez MJ, Davies JS, Thompson NM, Aguilar E, Pinilla L, Wells T, Dieguez C, Tena-Sempere M. Comparative analysis of the effects of ghrelin and unacylated ghrelin on luteinizing hormone secretion in male rats. Endocrinology 2006;147:2374–2382. [PubMed: 16455774]
31. Mason AO, Greives TJ, Scotti MA, Levine J, Frommeyer S, Ketterson ED, Demas GE, Kriegsfeld LJ. Suppression of kisspeptin expression and gonadotropic axis sensitivity following exposure to inhibitory day lengths in female Siberian hamsters. Horm Behav 2007;52:492–498. [PubMed: 17706968]
32. Matsui H, Takatsu Y, Kumano S, Matsumoto H, Ohtaki T. Peripheral administration of metastin induces marked gonadotropin release and ovulation in the rat. Biochem Biophys Res Commun 2004;320:383–388. [PubMed: 15219839]
33. Mead EJ, Maguire JJ, Kuc RE, Davenport AP. Kisspeptins: a multifunctional peptide system with a role in reproduction, cancer and the cardiovascular system. Br J Pharmacol 2007;151:1143–1153. [PubMed: 17519946]
34. Mead EJ, Maguire JJ, Kuc RE, Davenport AP. Kisspeptins are novel potent vasoconstrictors in humans, with a discrete localization of their receptor, G protein-coupled receptor 54, to atherosclerosis-prone vessels. Endocrinology 2007;148:140–147. [PubMed: 17023533]
35. Messager S, Chatzidaki EE, Ma D, Hendrick AG, Zahn D, Dixon J, Thresher RR, Malinge I, Lomet D, Carlton MB, Colledge WH, Caraty A, Aparicio SA. Kisspeptin directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54. Proc Natl Acad Sci U S A 2005;102:1761–1766. [PubMed: 15665093]
36. Muir AI, Chamberlain L, Elshourbagy NA, Michalovich D, Moore DJ, Calamari A, Szekeres PG, Sarau HM, Chambers JK, Murdock P, Steplewski K, Shabon U, Miller JE, Middleton SE, Darker JG, Larminie CG, Wilson S, Bergsma DJ, Emson P, Faull R, Philpott KL, Harrison DC. AXOR12, a novel human G protein-coupled receptor, activated by the peptide KiSS-1. J Biol Chem 2001;276:28969–28975. [PubMed: 11387329]
37. Navarro VM, Fernandez-Fernandez R, Castellano JM, Roa J, Mayen A, Barreiro ML, Gaytan F, Aguilar E, Pinilla L, Dieguez C, Tena-Sempere M. Advanced vaginal opening and precocious activation of the reproductive axis by KiSS-1 peptide, the endogenous ligand of GPR54. J Physiol 2004;561:379–386. [PubMed: 15486019]
38. Navarro VM, Castellano JM, Fernandez-Fernandez R, Barreiro ML, Roa J, Sanchez-Criado JE, Aguilar E, Dieguez C, Pinilla L, Tena-Sempere M. Developmental and hormonally regulated messenger ribonucleic acid expression of KiSS-1 and its putative receptor, GPR54, in rat hypothalamus and potent luteinizing hormone-releasing activity of KiSS-1 peptide. Endocrinology 2004;145:4565–4574. [PubMed: 15242985]
39. Navarro VM, Tena-Sempere M. The KiSS-1/GPR54 system: putative target for endocrine disruption of reproduction at hypothalamic-pituitary unit? Int J Androl 2008;31:224–232. [PubMed: 17971159]
40. Ohtaki T, Shintani Y, Honda S, Matsumoto H, Hori A, Kanehashi K, Terao Y, Kumano S, Takatsu Y, Masuda Y, Ishibashi Y, Watanabe T, Asada M, Yamada T, Suenaga M, Kitada C, Usuki S, Kurokawa T, Onda H, Nishimura O, Fujino M. Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. Nature 2001;411:613–617. [PubMed: 11385580]
41. Parhar IS, Ogawa S, Sakuma Y. Laser-captured single digoxigenin-labeled neurons of gonadotropin-releasing hormone types reveal a novel G protein-coupled receptor (Gpr54) during maturation in cichlid fish. Endocrinology 2004;145:3613–3618. [PubMed: 15155576]
42. Pielecka-Fortuna J, Chu Z, Moenter SM. Kisspeptin acts directly and indirectly to increase gonadotropin-releasing hormone neuron activity and its effects are modulated by estradiol. Endocrinology 2008;149:1979–1986. [PubMed: 18162521]
43. Popa SM, Clifton DK, Steiner RA. The Role of Kisspeptins and GPR54 in the Neuroendocrine Regulation of Reproduction. Annu Rev Physiol 2008;70:213–238. [PubMed: 17988212]

44. Revel FG, Saboureau M, Masson-Pevet M, Pevet P, Mikkelsen JD, Simonneaux V. Kisspeptin mediates the photoperiodic control of reproduction in hamsters. Curr Biol 2006;16:1730–1735. [PubMed: 16950111]
45. Richard N, Galmiche G, Corvaisier S, Caraty A, Kottler ML. KiSS-1 and GPR54 genes are co-expressed in rat gonadotrophs and differentially regulated in vivo by oestradiol and gonadotrophin-releasing hormone. J Neuroendocrinol 2008;20:381–393. [PubMed: 18208554]
46. Ringel MD, Hardy E, Bernet VJ, Burch HB, Schuppert F, Burman KD, Saji M. Metastin receptor is overexpressed in papillary thyroid cancer and activates MAP kinase in thyroid cancer cells. J Clin Endocrinol Metab 2002;87:2399. [PubMed: 11994395]
47. Roa J, Vigo E, Castellano JM, Gaytan F, Navarro VM, Aguilar E, Dijcks FA, Ederveen AG, Pinilla L, van Noort PI, Tena-Sempere M. Opposite Roles of Estrogen Receptor (ER) {alpha} and ER{beta} in the Modulation of Luteinizing Hormone Responses to Kisspeptin in the Female Rat: Implications for the Generation of the Preovulatory Surge. Endocrinology. 2008
48. Rometo AM, Krajewski SJ, Voytko ML, Rance NE. Hypertrophy and increased kisspeptin gene expression in the hypothalamic infundibular nucleus of postmenopausal women and ovariectomized monkeys. J Clin Endocrinol Metab 2007;92:2744–2750. [PubMed: 17488799]
49. Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno JSJ, Shagoury JK, Bo-Abbas Y, Kuohung W, Schwinof KM, Hendrick AG, Zahn D, Dixon J, Kaiser UB, Slaugenhaupt SA, Gusella JF, O'Rahilly S, Carlton MB, Crowley WFJ, Aparicio SA, Colledge WH. The GPR54 gene as a regulator of puberty. N Engl J Med 2003;349:1614–1627. [PubMed: 14573733]
50. Seminara SB, Dipietro MJ, Ramaswamy S, Crowley WFJ, Plant TM. Continuous human metastin 45-54 infusion desensitizes G protein-coupled receptor 54-induced gonadotropin-releasing hormone release monitored indirectly in the juvenile male Rhesus monkey (Macaca mulatta): a finding with therapeutic implications. Endocrinology 2006;147:2122–2126. [PubMed: 16469799]
51. Seminara SB. Kisspeptin in reproduction. Semin Reprod Med 2007;25:337–343. [PubMed: 17710729]
52. Shahab M, Mastronardi C, Seminara SB, Crowley WF, Ojeda SR, Plant TM. Increased hypothalamic GPR54 signaling: a potential mechanism for initiation of puberty in primates. Proc Natl Acad Sci U S A 2005;102:2129–2134. [PubMed: 15684075]
53. Silvestre RA, Egido EM, Hernandez R, Marco J. Kisspeptin-13 inhibits insulin secretion without affecting glucagon or somatostatin release: study in the perfused rat pancreas. J Endocrinol 2008;196:283–290. [PubMed: 18252951]
54. Smith JT, Dungan HM, Stoll EA, Gottsch ML, Braun RE, Eacker SM, Clifton DK, Steiner RA. Differential regulation of KiSS-1 mRNA expression by sex steroids in the brain of the male mouse. Endocrinology 2005;146:2976–2984. [PubMed: 15831567]
55. Smith JT, Cunningham MJ, Rissman EF, Clifton DK, Steiner RA. Regulation of Kiss1 gene expression in the brain of the female mouse. Endocrinology 2005;146:3686–3692. [PubMed: 15919741]
56. Smith JT, Acohido BV, Clifton DK, Steiner RA. KiSS-1 neurones are direct targets for leptin in the ob/ob mouse. J Neuroendocrinol 2006;18:298–303. [PubMed: 16503925]
57. Smith JT, Popa SM, Clifton DK, Hoffman GE, Steiner RA. Kiss1 neurons in the forebrain as central processors for generating the preovulatory luteinizing hormone surge. J Neurosci 2006;26:6687–6694. [PubMed: 16793876]
58. Stafford LJ, Xia C, Ma W, Cai Y, Liu M. Identification and characterization of mouse metastasis-suppressor KiSS1 and its G-protein-coupled receptor. Cancer Res 2002;62:5399–5404. [PubMed: 12359743]
59. Teles MG, Bianco SD, Brito VN, Trarbach EB, Kuohung W, Xu S, Seminara SB, Mendonca BB, Kaiser UB, Latronico AC. A GPR54-activating mutation in a patient with central precocious puberty. N Engl J Med 2008;358:709–715. [PubMed: 18272894]
60. Thompson EL, Patterson M, Murphy KG, Smith KL, Dhillo WS, Todd JF, Ghatei MA, Bloom SR. Central and peripheral administration of kisspeptin-10 stimulates the hypothalamic-pituitary-gonadal axis. J Neuroendocrinol 2004;16:850–858. [PubMed: 15500545]

61. Yamada S, Uenoyama Y, Kinoshita M, Iwata K, Takase K, Matsui H, Adachi S, Inoue K, Maeda KI, Tsukamura H. Inhibition of metastin (kisspeptin-54)-GPR54 signaling in the arcuate nucleus-median eminence region during lactation in rats. Endocrinology 2007;148:2226–2232. [PubMed: 17289848]

62. Yan C, Wang H, Boyd DD. KiSS-1 represses 92-kDa type IV collagenase expression by down-regulating NF-kappa B binding to the promoter as a consequence of Ikappa Balpha -induced block of p65/p50 nuclear translocation. J Biol Chem 2001;276:1164–1172. [PubMed: 11060311]

Table 1

Current and Recommended Symbols for the Kisspeptin Gene and Protein

Species	Current Terminology		Recommended Terminology	
	Gene/mRNA	**Peptide**	**Gene/mRNA**	**Peptide**
Rodent and other non-human species	KiSS-1 KiSS1 Kiss-1 Kiss1 (typically italicized for the gene and not for mRNA) **MGI format: *Kiss1***	**Mature Peptide:** metastin kisspeptin kisspeptin-54 KiSS-1 peptide KiSS-1 protein **Bioactive Fragments:** kisspeptin-145, -14, -13, -10 Kp-145, -14, -13, -10 kisspeptin-1 (68-121) kisspeptin/metastin (112-121) KiSS-1 peptide KiSS-1 protein	*Kiss1/Kiss1* mRNA	**Mature Peptide:** kisspeptin Kiss1 **Bioactive Fragments:** kisspeptin-*fragment length* (e.g. Kisspeptin-10) Kp-*fragment length* (e.g., Kp-10)
Human	KiSS-1 KiSS1 (typically italicized for the gene and not for mRNA) **HGNC symbol: *KISS1***	**Mature Peptide:** metastin kisspeptin KiSS-1 **Bioactive Fragments:** Kisspeptin-145, -14, -13, -10 Kp-145, -14, -13, -10 Human metastin 45-54	*KISS1/KISS1* mRNA	**Mature Peptide:** Kisspeptin KISS1 **Bioactive Fragments:** kisspeptin-*fragment length* (e.g. Kisspeptin-10) KP-*fragment length* (e.g., KP-10)

Table 2

Current and Recommended Terminology for the Kisspeptin Receptor Gene and Protein

Species	Current Terminology		Recommended Terminology	
	Gene/mRNA	**Peptide**	**Gene/mRNA**	**Peptide**
Rodent and other non-human species	GPR54 *Gpr54* **MGI format: *Kiss1r***	GPR54 Kiss1R	*Kiss1r/Kiss1r* mRNA	kisspeptin (or Kiss1) receptor Kiss1r
Human	AXOR12 HOT7T175 *GPR54* *KiSS1R* **HGNC format: *KISS1R***	GPR54 KiSS1 (GPR54)	*KISS1R/KISS1R* mRNA	kisspeptin (or KISS1) receptor KISS1R