



Role of Kisspeptin in Puberty in Humans

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Authors' contributions

This work was carried out in collaboration between both authors. Author RK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author MKM managed editing and analyses of the study. Both authors read and approved the final manuscript.

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ABSTRACT

Kisspeptin or GPR-54 is a product of KISS 1 gene regulating the production of gonadotropin releasing hormone (GnRH), luteinizing (LH) as well follicle stimulating hormone (FSH). Both LH and FSH are important hormones for reproduction in animals as well in humans. The recognition of Kisspeptin has a landmark bearing in reproductive biology. Few recent pilot studies have convincingly proven it to be a promising molecule in treating infertile couples especially those having hypogonadotropic hypogonadism not responding to conventional treatment.

Keywords: *Kisspeptin; GPR-54; gonadotropin releasing hormone; luteinizing hormone; follicle stimulating hormone; hypogonadotropic hypogonadism.*

1. INTRODUCTION

Reproduction is essential for continuation of species, human as well as others. The endocrinology of human reproduction is complex and only partially understood. Until recently

GnRH was supposed to be the main hormone regulating human reproduction through its Tropic hormones; LH and FSH. Onset of puberty, sexual maturation and reproduction are regulated by hypothalamic pituitary gonadal axis (HPG) whereby GnRH produced in preoptic hypothalamus stimulate pulsatile release of FSH

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and LH from anterior pituitary which in turn stimulate gametogenesis and sex steroid production. Precise mechanism for reactivation of HPG axis characterized by pulsatile release GnRH which marks the onset of puberty is not known. The recent studies however have identified near proteins identified as kisspeptin which of course plays a vital role in the upstream regulation of GnRH.

1.1 Kisspeptin Synthesis and Secretion

Kisspeptin is product of KISS1 gene located on long arm of chromosome 1. KISS 1 was named after the location where it was first discovered (home of Hershey's Kisses). Kisspeptin is basically derived as a product of cleavage of 145 amino acid chain into a smaller 54 amino acid long protein [1] known as kisspeptin 54. There are other products of this protein in which parent protein consists of 13 and 14 amino acids and hence named accordingly kisspeptin13 and kisspeptin14. The carboxy terminal of these fragments consists of a highly conserved chain of 10 amino acids [2] across species. In humans, kisspeptin has been found to be expressed in hypothalamus principally in the arcuate nucleus (ARC), the anteroventral periventricular nucleus (AVPV) and periventricular nucleus (PEN), apart from brain this is also expressed in placenta, ovaries, testes, pancreas and intestine [3,4,5].

2. MECHANISM OF ACTION

Kisspeptin exerts function via its receptor GPR54 (Kiss1r), a G protein coupled receptor initially described in the rodent hypothalamus predominantly in GnRH secreting neurons, similar findings have been confirmed among sheep and monkeys [6,7], in addition to hypothalamus these receptors are expressed on hippocampus, anterior pituitary, pancreas, liver and adipose tissues [3,4,5]. In both rats and humans, it exerts its action by activating the downstream pathways ERK1, ERK 2, arachidonic acid hydrolysis and Ca^{2+} mobilization. GnRH neurons are located in pituitary gland and other areas, they respond more briskly to inputs from kisspeptin as compared to pituitary gonadotropes [8]. Interaction of kisspeptin with its receptor at GnRH neurons not only causes depolarization but expression of kisspeptin genes in these neurons. It is the interaction between kisspeptin and GPR54 at GnRH neurons that plays a crucial role in puberty and reproduction along with tumor suppression.

2.1 Regulation of Puberty

Puberty onset is characterized by pulsatile release of GnRH with downstream effect on pituitary gonadotropin secreting cells via G-protein-coupled receptor leading to pulsatile LH and FSH release. This GnRH pulse is regulated by various upstream signaling pathways among which role of KNDy system (Kisspeptin, Neurokinin B and dynorphin) is pivotal. Kisspeptin considered the primary stimulator of GnRH with neurokinin B (stimulatory) and dynorphin (inhibitory) fine tuning its effect.

2.2 Effect of Kisspeptin on Sex Steroids

Kisspeptin directly stimulate the secretion of GnRH from anterior pituitary (Fig. 1), as GnRH can't be directly measured in peripheral circulation hence LH pulse remains the surrogate marker of GnRH pulse as each GnRH pulse is associated with a LH and FSH pulse, LH being more closely related to GnRH secretion as compared to FSH [8]. Effect of Kisspeptin-54 on HPG axis was tested by administering Kisspeptin-54 in healthy men by via intravenous infusion at a dose of 0.023 mg/kg/min for 90 min, they found a robust and dose-dependent increase from 0.001 mg/kg/min to 0.07 mg/kg/min in LH, and less marked rises in FSH and testosterone [9].

Although direct stimulation seems to be the principal mechanism of LH/FSH secretion studies have also proven that direct stimulation of gonadotrophs also takes place. The evidence has come from studies on pituitary explants expressing kiss1r secreting gonadotropins when treated with kisspeptin [10]. Navarrao et al showed that the kiss1 and kiss1r mRNA were remarkably increased in hypothalamus during puberty [11]. The GnRH neurons discharges were markedly increased at the onset of puberty in mice right from 25% (juvenile), to 50% (prepubertal) and >90% (pubertal) suggesting increasing sensitivity to kisspeptin as the age [11].

Two independent groups identified 'inactivating' point mutations and deletions in kiss1r that were associated with impaired pubertal development in some patients with hypogonadotropic hypogonadism [12,13]. Seminara and Roux also noticed that the family members with idiopathic hypogonadotropic hypogonadism (IHH) had mutation in kiss1r. They created a

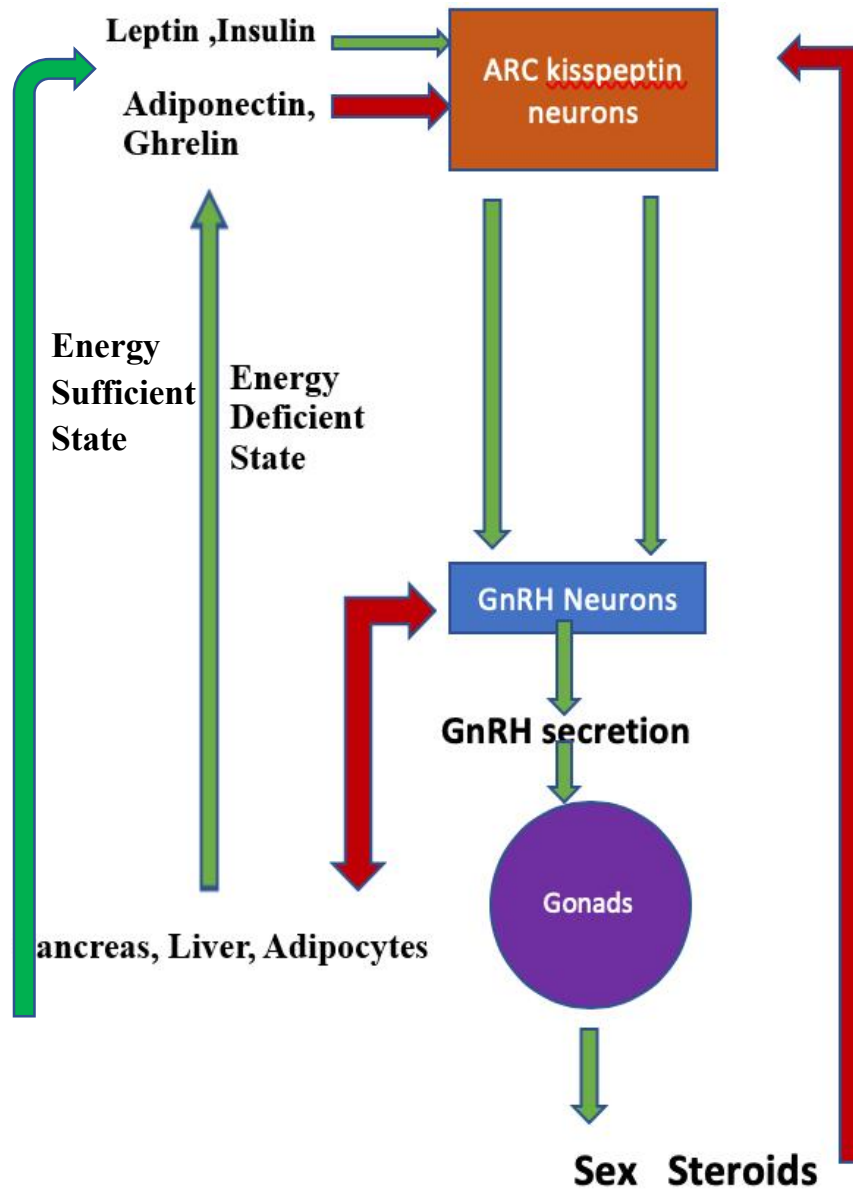


Fig. 1. Depicting energy balance and reproduction by kisspeptin and GnRH neurons: kisspeptin neurons stimulate GnRH neurons which in turn stimulate secretion of FSH/LH
Sex steroids (estrogen/ progesterone/ testosterone) have negative feedback control on kisspeptin neurons, Kisspeptin neurons are also affected by leptin and insulin (excitatory) and Ghrelin and adiponectin (inhibitory). Green and red are excitatory and Inhibitory inputs respectively. (ARC- Arcuate Nucleus)

mouse model deficient in kiss1r and noticed their phenotype, it was noticed that they were not different from IHH, male mice had small testis and female mice had small ovaries as well as absent follicular maturation and small vaginal opening. When challenged with exogenous GnRH a phenotypic reversal to normal was seen in this model. These findings not only proved that kiss1r exerts a powerful effect on the

reproductive milieu but also established that kisspeptin, which has a strong affinity to this receptor was established as a powerful determinant of puberty. Their findings were further strengthened by Gottsch et al. who injected kisspeptin directly into the lateral ventricle in mouse and observed a profound increase in LH and FSH [14]. Furthermore, administration of a GnRH antagonist (acyclin)

prevented kisspeptin's stimulatory effect, proving that kisspeptin works through GnRH neurons. In a prospective, randomized, double-blinded, parallel design study conducted on females of hypothalamic amenorrhea [15], they received twice-daily S/C injections of kisspeptin (6.4 nmol/kg) or 0.9% saline (n = 5 per group) for 2 weeks. Parameters for response were gonadotropin level, LH pulsatility and estradiol level. It was found that administration of kisspeptin acutely increased the LH/FSH concentration, this effect however was duration dependent and weaned off by 14th day of the trial. However, they remained responsive to GnRH stimulation on day 14th even. There was however no effect on LH pulsatility and ultrasound assessment of reproduction in subjects.

Similarly, 6 males diagnosed with IHH when injected with kisspeptin and GnRH showed remarkable increase in LH and spontaneous LH pulsatility, those who had sustained reversal (4 out of 6) responded to exogenous kisspeptin, whereas those who had relapse (2 out of 6) were those who did not respond to kisspeptin [16].

3. EFFECT OF GONADOTROPINS ON KISSPEPTIN/GNRH

Estradiol (Fig. 1) exerts a potent differential effect on kiss1 mRNA in both arcuate nucleus (ARC) and rostral periventricular region of the third ventricle (RP3V). The kisspeptin neurons were stimulated in RP3V and inhibited in ARC [16], simultaneous expression of the neuropeptides neurokinin B (NKB) and dynorphin (Dyn) within ARC kisspeptin neurons and control of these neurons (KND is responsible for inhibition). Animal model (sheep) support the KNDy hypothesis as NKB receptor antagonists reduces LH pulse frequency [17,18] and NKB or dynorphin receptor antagonists increase LH pulses.

4. EFFECT OF METABOLIC STATUS ON KISSPEPTIN/GNRH

Relation between pre-adolescent weight gain and age of pubertal onset has been known since long ago. Kisspeptin signaling and cascade downstream is extremely sensitive to metabolic status. Animal studies done in mouse have depicted positive effect of leptin, insulin, melanocortin and glucagon like peptide 1 with reversal of reduced kiss1 mRNA level in short-term fasted prepubertal rats with leptin

administration [19]. On the contrary increased levels of adiponectin and ghrelin seen in fasting states have been found to be associated with decreased expression of kisspeptin-GnRH signaling (Fig. 1).

5. CONCLUSIONS

Puberty, a major developmental milestone, is characterized by complete activation of gonadal axis brought about by GnRH pulse generation which is central HPG axis. Kisspeptin is the neurohormonal factor controlling the upstream activation of this axis during puberty with abnormalities in Kiss1-GPR54 signaling implicated various forms of infertility (delayed puberty, idiopathic hypogonadotropic hypogonadism). Regulation of Kisspeptin pathway with various activators and inhibitors is being studied presently. Most of these studies regarding leptin, ghrelin, insulin and adiponectin has been done on non-human primates and their role in human development is still unclear. Further studies are needed to delineate the exact pathway and its translation into management of pubertal disorders and infertility.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mead EJ, Maguire JJ, Kuc RE, Davenport AP. Kisspeptins: A multifunctional peptide system with a role in reproduction, cancer and the cardiovascular system. *British Journal of Pharmacology*. 2007;151(8): 1143-53.
2. Pasquier J, Kamech N, Lafont AG, Vaudry H, Rousseau K, Dufour S. Molecular evolution of GPCRs: Kisspeptin/kisspeptin receptors. *Journal of Molecular Endocrinology*. 2014;52(3):T101-17.
3. Kotani M, Detheux M, Vandenbogaerde A, Communi D, Vanderwinden JM, Le Poul E, Brézillon S, Tyldesley R, Suarez-Huerta N,

- Vandeput F, Blanpain C. The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. *Journal of Biological Chemistry*. 2001; 276(37):34631-6.
4. Muir AI, Chamberlain L, Elshourbagy NA, Michalovich D, Moore DJ, Calamari A, Szekeres PG, Sarau HM, Chambers JK, Murdock P, Steplewski K. AXOR12, a novel human G protein-coupled receptor, activated by the peptide KiSS-1. *Journal of Biological Chemistry*. 2001;276(31):28969-75.
 5. Ohtaki T, Shintani Y, Honda S, Matsumoto H, Hori A, Kanehashi K, Terao Y, Kumano S, Takatsu Y, Masuda Y, Ishibashi Y. Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. *Nature*. 2001; 411(6837):613-7.
 6. 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. *Proceedings of the National Academy of Sciences*. 2005; 102(6):2129-34.
 7. Kim W, Jessen HM, Auger AP, Terasawa E. Postmenopausal increase in KiSS-1, GPR54, and luteinizing hormone releasing hormone (LHRH-1) mRNA in the basal hypothalamus of female rhesus monkeys. *Peptides*. 2009;30(1):103-10.
 8. George JT, Veldhuis JD, Tena-Sempere M, Millar RP, Anderson RA. Exploring the pathophysiology of hypogonadism in men with type 2 diabetes: Kisspeptin-10 stimulates serum testosterone and LH secretion in men with type 2 diabetes and mild biochemical hypogonadism. *Clinical Endocrinology*. 2013 Jul;79(1):100-4.
 9. Dhillon 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. *The Journal of Clinical Endocrinology & Metabolism*. 2005;90(12): 6609-15.
 10. Kotani M, Detheux M, Vandenberghe A, Communi D, Vanderwinden JM, Le Poul E, Brézillon S, Tyldesley R, Suarez-Huerta N, Vandeput F, Blanpain C. The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. *Journal of Biological Chemistry*. 2001; 276(37):34631-6.
 11. Navarro VM, Gottsch ML, Chavkin C, Okamura H, Clifton DK, Steiner RA. Regulation of gonadotropin-releasing hormone secretion by kisspeptin/dynorphin/neurokinin B neurons in the arcuate nucleus of the mouse. *Journal of Neuroscience*. 2009;29(38):11859-66.
 12. 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. *Proceedings of the National Academy of Sciences*. 2003; 100(19):10972-6.
 13. Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno Jr JS, Shagoury JK, Bo-Abbas Y, Kuohung W, Schwinof KM, Hendrick AG, Zahn D. The GPR54 gene as a regulator of puberty. *New England Journal of Medicine*. 2003;349(17):1614-27.
 14. Gottsch ML, Navarro VM, Zhao Z, Glidewell-Kenney C, Weiss J, Jameson JL, Clifton DK, Levine JE, Steiner RA. Regulation of Kiss1 and dynorphin gene expression in the murine brain by classical and nonclassical estrogen receptor pathways. *Journal of Neuroscience*. 2009; 29(29):9390-5.
 15. Jayasena CN, Nijher GM, Chaudhri OB, Murphy KG, Ranger A, Lim A, Patel D, Mehta A, Todd C, Ramachandran R, Salem V. Subcutaneous injection of kisspeptin-54 acutely stimulates gonadotropin secretion in women with hypothalamic amenorrhea, but chronic administration causes tachyphylaxis. *The Journal of Clinical Endocrinology & Metabolism*. 2009;94(11):4315-23.
 16. Lippincott MF, Chan YM, Delaney A, Rivera-Morales D, Butler JP, Seminara SB. Kisspeptin responsiveness signals emergence of reproductive endocrine activity: implications for human puberty. *The Journal of Clinical Endocrinology & Metabolism*. 2016;101(8):3061-9.
 17. Smith JT, Li Q, Pereira A, Clarke IJ. Kisspeptin neurons in the ovine arcuate nucleus and preoptic area are involved in the preovulatory luteinizing hormone surge. *Endocrinology*. 2009;150(12):5530-8.
 18. Goodman RL, Lehman MN, Smith JT, Coolen LM, De Oliveira CV,

- Jafarzadehshirazi MR, Pereira A, Iqbal J, Caraty A, Ciofi P, Clarke IJ. Kisspeptin neurons in the arcuate nucleus of the ewe express both dynorphin A and neurokinin B. *Endocrinology*. 2007;148(12):5752-60.
19. Wahab F, Atika B, Ullah F, Shahab M, Behr R. Metabolic impact on the hypothalamic kisspeptin-Kiss1r signaling pathway. *Frontiers in endocrinology*. 2018; 9:123.

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