

Review Article

The role of kisspeptin signalling in the hypothalamic-pituitary-gonadal axis

Carol Cardona Attard

Abstract

Kisspeptin is a hypothalamic peptide hormone, which plays a crucial role in puberty and fertility control by stimulating the release of gonadotrophin-releasing hormone, which in turn stimulates the release of luteinizing hormone and follicle stimulating hormone. It also interacts with neuropeptides neurokinin B and dynorphin A, and is under negative and positive feedback influences relayed by gonadal sex steroids. Loss of kisspeptin signalling results in hypogonadotrophic hypogonadism and impaired puberty. Kisspeptin expression and secretion is also affected by metabolic status and stress. Several studies have indicated a potential role for kisspeptin in the treatment of disorders causing hypogonadotrophic hypogonadism. This review aims to summarize the importance of kisspeptin and its role in the hypothalamic-pituitary-gonadal axis.

Keywords

kisspeptin, gonadotrophin-releasing hormone, gonadotrophins, fertility, puberty

Carol Cardona Attard MD, MRCP (UK)

Diabetes and Endocrine Centre

Mater Dei Hospital

Msida, Malta

Department of Medicine

University of Malta

Medical School

Msida, Malta

carol-diane.attard@gov.mt

**Corresponding Author*

Introduction

Kisspeptin is a hypothalamic peptide encoded by the *KISS1* gene, which is found on chromosome 1q32, and is a powerful stimulator of the hypothalamic-pituitary-gonadal (HPG) axis. It is involved in puberty onset and fertility control,¹ and appears to be important for sexual development and differentiation in the early postnatal period, possibly through regulation of postnatal testosterone secretion.² It acts upstream to gonadotrophin-releasing hormone (GnRH) and is cleaved from a 145-amino acid precursor peptide into a 54-amino acid peptide, which can be further cleaved into 14, 13 and 10-amino acid peptides. These carboxy-terminal RF-amide peptides are collectively called kisspeptins.¹

Kisspeptin binds to the G-protein coupled receptor 54 or *KISS1* receptor (*KISS1R* in humans/*Kiss1r* in rodents), expressed on GnRH neurons (also widely expressed within both cortical and subcortical regions and peripherally). It stimulates the pulsatile secretion of GnRH from GnRH neurons into the portal circulation, which will then stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the gonadotrophs in the anterior pituitary.¹

Kisspeptin neurons and sexual dimorphism

In humans, kisspeptin neurons reside in the hypothalamic rostral preoptic area, in the infundibular (arcuate) nucleus, in the anterior parvocellular and magnocellular

subdivisions of the paraventricular nucleus and in the ventral and rostral periventricular hypothalamic nucleus.³ Infundibular and rostral kisspeptin neurons are in close apposition with GnRH neurons. Kisspeptin neurons in the infundibular nucleus also express neurokinin B and dynorphin A, and are thus called KNDy neurons. Neurokinin B and dynorphin A autosynaptically control kisspeptin pulsatile secretion and thus GnRH release, by binding to the neurokinin B receptor (stimulatory) and kappa opioid peptide receptor (inhibitory) respectively, which are found on KNDy cells. GnRH neurons do not express the oestrogen, progesterone or androgen receptors, which are however found on KNDy neurons. This suggests that KNDy neurons are responsible for relaying sex hormone negative and positive feedback, and thus regulating pulsatile kisspeptin release.¹ The oestrogen receptor alpha (ER α) is fundamental for positive feedback, but was not found to be important for negative feedback on GnRH/LH secretion in adult female mice.⁴

Females have appreciably more kisspeptin fibres and cell bodies in the infundibular nucleus as well as a significantly greater number of kisspeptin fibres in the ventral periventricular area compared to men. In addition, expression of kisspeptin cell bodies in the rostral periventricular zone is seen in females only.¹ This greater number of kisspeptin neurons in females will allow them to secrete more kisspeptin, which will enable them to produce the LH surge.² Kisspeptin can reset the GnRH pulse generator in men i.e. kisspeptin can induce an LH pulse regardless of the timing of previous endogenous pulses.¹ This is not seen in women across the different menstrual cycle phases, which could be due to changes in the sex hormone levels along the cycle. Different kisspeptin responses

depending on the menstrual cycle phase were noted in the study by Chan *et al*, and it appeared that kisspeptin tone was greater in the early follicular phase in contrast to the rest of the cycle phases.⁵

Kisspeptin and the reproductive axis

Kisspeptin's effect on LH secretion is greater, often causing a 2 to 3-fold rise in most circumstances with a robust increase in both pulse frequency and amplitude, while its effect on FSH release is of a lower magnitude and less consistent.⁶⁻⁹ The gonadotrophin secretory pattern difference in response to kisspeptin could be due to variations in the secretory pattern between LH and FSH, being more constitutive for FSH; differences in the effect of kisspeptins on the GnRH secretory pattern, where induction of high frequency GnRH pulses will preferentially stimulate LH; and differences in regulatory influences of gonadal peptides such as inhibins, which regulate FSH release.¹⁰

Kisspeptin neurons in the infundibular nucleus were found to become hypertrophied and harboured more KISS1 messenger ribonucleic acid (mRNA) in post-menopausal women compared to pre-menopausal women,¹¹ with increased expression of neurokinin B¹² and lack of dynorphin A signalling.¹ In a recent study, the number of kisspeptin-immunoreactive neurons within the infundibular nucleus of humans was found to be significantly higher in the infant/prepubertal and elderly (58-90 year olds) periods rather than during the adult period (22-44 year olds).¹³ This means that oestrogen (or testosterone in males) suppresses kisspeptin and neurokinin B expression and release, whereas dynorphin A would be upregulated through negative feedback on the KNDy neurons, leading to a reduction in tonic GnRH and gonadotrophin

release, as occurs during the pre-ovulatory follicular phase.¹ Only a partial inhibition of KISS1 mRNA was noted in sheep following progesterone replacement.¹⁰

A change to positive feedback, which is associated with an increase in the oestrogen levels, occurs in the late follicular phase to induce the LH surge and ovulation.¹ Many studies have shown that kisspeptin is essential for the LH surge. KISS1 mRNA increased in the anteroventral periventricular (AVPV) nucleus of ovariectomized rats at the time of the oestrogen and progesterone induced LH surge.¹⁴ Exogenous kisspeptin induced oocyte maturation and an LH surge during an FSH/GnRH antagonist *in-vitro* fertilisation protocol.¹⁵ Moreover, KISS1 and Kiss1r knock-out (KO) mice fail to mount this pre-ovulatory LH surge.¹⁶ An intrinsic circadian Kiss-clock in the hypothalamic AVPV nucleus of female mice acting in combination with the suprachiasmatic nucleus may be leading to a circadian pattern of kisspeptin gene expression and neuronal activation in females.¹⁷ However, this circadian activation of kisspeptin neurons was found to rely on the presence of oestrogen, indicating that the LH surge is oestrogen dependent.^{2,17} Changes in neurokinin B and dynorphin A levels may also contribute to the kisspeptin mediated LH surge.¹ A recent study has demonstrated that the positive feedback of progesterone is likewise required for the kisspeptin neuronal activation and induction of the LH surge.¹⁸

KISS1 and KISS1R genes were noted to be expressed in pituitary gonadotrophs, while gonadotrophins (LH more than FSH) were secreted from pituitary explants on treatment with kisspeptin, indicating that kisspeptin may directly stimulate the release of LH and FSH from gonadotrophs.¹⁹⁻²⁰ However, the principal mechanism of

gonadotrophin secretion still appears to be through stimulation of GnRH.²¹

Kisspeptin may also have a role in direct signalling on the ovary. This is suggested by a study done in mice where haplo-insufficiency of the Kiss1r resulted in a premature deterioration of the ovulatory rate as well as progressive loss of pre-antral and antral follicles and oocytes, resulting in a decline in fertility, atrophic ovaries and a state of premature ovarian failure. A decrease in ovarian Kiss1r mRNA expression was noted in the absence of a decline in gonadotrophins. FSH actually increased due to follicular loss. On the other hand, Kiss1r null mice, which have arrested follicular development and are anovulatory, lacked normal ovulatory responses on standard gonadotrophin priming.²² Moreover, KISS1 and KISS1R mRNA have been found to be expressed in human gonads. Some studies in rats have shown that ovarian KISS1 expression increases during puberty and prior to ovulation under the influence of gonadotrophins, with a possible role of locally produced ovarian kisspeptin in ovulatory regulation.¹⁰ Kisspeptin has also been shown to potentiate the effect of human chorionic gonadotrophin on testosterone release from the testes, and it can increase spermatozoa motility and fertilization capacity.²³

Role of kisspeptin in puberty

Inactivating mutations or KO of kisspeptin or its receptor result in hypogonadotrophic hypogonadism (HH) as well as impaired puberty/sexual maturation and infertility,^{2,24-25} while activating mutations or administration of exogenous kisspeptin result in precocious puberty.²⁶⁻²⁸ Loss of kisspeptin (or its receptor) is responsible for approximately 2% of HH cases in humans.²⁹ In a study done in mice,

there is an increase in the amount of GnRH neurons which depolarise in response to kisspeptin, from 27% in juvenile, to 44% in prepubertal, to >90% in adult mice, which means that GnRH neurons become more sensitive to kisspeptin during puberty. KISS1 mRNA increased from juvenile to adult mice in the AVPV nucleus, suggesting an increase in kisspeptin tone.³⁰

Kiss1r mRNA expression is also increased,³¹ which may play an important role in puberty by increasing the sensitivity of GnRH neurons to kisspeptin. Increase in Kiss1r expression appears to occur earlier in female than in male rats, providing a possible explanation for earlier puberty in females.² Furthermore, during puberty, there is an increase in the number of kisspeptin neurons and synaptic contacts with GnRH neurons.^{10, 32} In mice, the activation of kisspeptin expression during puberty appears to be driven by oestrogen; therefore, it appears that kisspeptin may require some degree of ovarian activation, which however, may not be the case in humans.¹⁰ In a study by Guerriero *et al.*, the response of GnRH to kisspeptin was noted to switch from ovarian steroid independent (pre-pubertal) to dependent during puberty in female rhesus monkeys.³³ A recent study has shown that the leptin - alpha-melanocyte stimulating hormone - kisspeptin - GnRH neuronal pathway in rodent models is involved in the metabolic control of puberty.³⁴ Because of the greater amount of adipose tissue present close to puberty, more leptin would be secreted leading to kisspeptin release.³⁵

Kisspeptin - link between reproduction and metabolic status

Reproduction requires sufficient amount of energy stores as it is highly metabolically demanding.³² Kisspeptin is

regulated by metabolic signals (e.g leptin, ghrelin and neuropeptide Y) and may sense energy stores, which then influences the pulsatile release of GnRH, thus providing a connection between nutritional/metabolic status and reproduction. Fasting and chronic undernutrition are associated with reduced kisspeptin and neurokinin B expression.¹ In contrast, prepubertal rats given a high fat diet, showed increased kisspeptin and neurokinin B expression as well as LH pulsatility, leading to precocious puberty. Kisspeptin expression is decreased in leptin deficiency or leptin receptor ablation, where gonadotrophin levels improve upon leptin or kisspeptin administration respectively. This suggests that leptin positively regulates kisspeptin expression.³⁶ Reduced kisspeptin expression and secretion may also be responsible for HH seen in patients with obesity and type 2 diabetes.¹ This is suggested by reduced hypothalamic KISS1 mRNA expression in a rat model of diabetes, with resultant low levels in gonadotrophins and sex hormones, which were corrected with kisspeptin administration.³⁷ Possible mechanisms for reduced kisspeptin signalling in obesity and diabetes include: a rise in oestrogen levels in obesity, which then feeds back negatively on kisspeptin secretion, leptin resistance, insulin resistance, hyperglycaemia as well as increased inflammation seen in diabetes.¹

Stress and its effect on kisspeptin

During stress and inflammation there is reduced expression of kisspeptin and Kiss1r as well as a reduction in kisspeptin responsiveness, leading to reduced gonadotrophin levels. This is partially mediated by the rise in corticotrophin releasing hormone and glucocorticoids. Moreover, stress during neonatal period/early stages of reproductive

development has been found to lead to reduced KISS1 mRNA levels during puberty with pubertal delay in rats, indicating that the developing kisspeptin system is vulnerable to immune and metabolic stressors.¹⁰

Kisspeptin in pregnancy and lactation

The levels of kisspeptin, secreted from syncytiotrophoblast placental cells, are elevated in pregnancy by 7000-fold. These persistently high circulating levels can possibly cause desensitization to the kisspeptin stimulatory effect on gonadotrophin secretion, resulting in partially suppressed gonadotrophin levels during pregnancy.¹⁰ Kisspeptin in gestation may also be important for trophoblast invasion, embryo implantation and maintenance of pregnancy.³ Moreover, a reduction in responsiveness to kisspeptin and repression of its expression was noted during lactation, leading to an overall suppression of the HPG axis in this phase.¹⁰

Therapeutic potential of kisspeptin

Given the effects of kisspeptin on the HPG axis, it may potentially be considered for the treatment of some conditions which induce HH. When given in hypothalamic amenorrhoea, kisspeptin can induce and increase LH pulsatility, with an increase in frequency and mass per pulse,³⁸ though it has a lower effect on FSH.⁸ Exogenous kisspeptin induced an increase in LH and testosterone in type 2 diabetes patients suffering from HH.⁹ It also stimulated LH secretion by 2.5-fold in patients with neurokinin B system defects (who also suffer from HH due to failure to stimulate kisspeptin).⁷ Kisspeptin plays a crucial role in hyperprolactinaemic anovulation and the resultant HH. This is because kisspeptin neurons express prolactin receptors, leading

to reduced kisspeptin expression in hyperprolactinaemia. Gonadotrophin secretion and ovarian cyclicity is restored on administration of kisspeptin.³⁹ It can also be used to stimulate oocyte maturation in women at high risk of developing ovarian hyperstimulation syndrome during *in-vitro* fertilization therapy.⁴⁰ On the other hand, kisspeptin can be used as antagonistic therapy (high doses and continuous infusions can cause KISS1R desensitisation) to decrease GnRH and LH pulsatility in polycystic ovary syndrome, early puberty and menopause.¹

Conclusion

It is evident that kisspeptin-KISS1R signalling is crucial to promote normal pulsatile GnRH and gonadotrophin secretion. This is important for sexual maturation and puberty as well as normal reproductive function and fertility.^{2, 41} It may also have a potential role in the treatment of certain disorders causing HH as described above.

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