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REVIEW ARTICLE

What is the master regulator of reproductive endocrinology? A sex-based functional review of the *KISS1-KISS1R* system

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Abstract

Kisspeptin, a peptide encoded by the KISS1 gene, and its receptor, KISS1R, have emerged as pivotal regulators of reproductive endocrinology. This review explores the multifaceted roles of the KISS1-KISS1R system in both male and female reproduction, from puberty onset to gametogenesis, ovulation, pregnancy, and lactation. In males, kisspeptin influences spermatogenesis through intratesticular signaling, modulating steroidogenesis and sperm function. In females, it regulates follicular development, oocyte maturation, and ovulation by modulating gonadotropin release and ovarian signaling pathways. Beyond reproduction, kisspeptin has been implicated in metabolic regulation, energy balance, and reproductive behavior, highlighting its broader physiological significance. Recent studies suggest potential clinical applications, including its use as a biomarker for early pregnancy detection and as a therapeutic agent for infertility, polycystic ovary syndrome, and hyperprolactinemia. In addition, kisspeptin analogs have demonstrated promise in treating hormone-dependent malignancies, such as prostate cancer, by suppressing the hypothalamic-pituitary-gonadal axis. Compared to other reproductive hormones, kisspeptin stands out as an upstream regulator, directly controlling gonadotropin-releasing hormone secretion and the entire reproductive hormonal cascade. Given its central role, further research is warranted to elucidate its precise mechanisms and optimize its clinical applications. The KISS1-KISS1R system is undeniably a master regulator of reproductive endocrinology, presenting exciting opportunities for therapeutic advancements in reproductive medicine.

Keywords: *Kisspeptin. KISS1 gene. KISS1R gene. Human reproduction. Reproductive physiology. Molecular mechanisms.*

¿Cuál es el regulador principal de la endocrinología reproductiva? Una revisión funcional del sistema KISS1-KISS1R con perspectiva de género

Resumen

La kisspeptina, un péptido codificado por el gen KISS1, y su receptor, KISS1R, se han identificado como reguladores clave de la endocrinología reproductiva. Esta revisión explora los diversos roles del sistema KISS1-KISS1R en la reproducción masculina y femenina, desde el inicio de la pubertad hasta la gametogénesis, la ovulación, el embarazo y la lactancia. En los hombres, la kisspeptina influye en la espermatogénesis mediante la señalización intratesticular, modulando la esteroidogénesis y la función espermática. En las mujeres, regula el desarrollo folicular, la maduración del ovocito y la ovulación, modulando la liberación de gonadotropinas y las vías de señalización ovárica. Más allá de la reproducción, se ha implicado

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a la kisspeptina en la regulación metabólica, el balance energético y el comportamiento reproductivo, destacando su importancia fisiológica general. Los estudios recientes sugieren potenciales aplicaciones clínicas, incluyendo su uso como biomarcador para la detección temprana del embarazo y como agente terapéutico para la infertilidad, el síndrome de ovario poliquístico y la hiperprolactinemia. Además, los análogos de la kisspeptina se han mostrado prometedores en el tratamiento de neoplasias dependientes de hormonas, como el cáncer de próstata, al suprimir el eje hipotálamo-hipófisis-gónadas. Dado su papel central, se requiere más investigación para entender sus mecanismos precisos y mejorar sus aplicaciones clínicas. El sistema KISS1-KISS1R es, sin duda, un regulador principal de la endocrinología reproductiva, que ofrece emocionantes oportunidades para avances terapéuticos en medicina reproductiva.

Palabras clave: *Kisspeptina. Gen KISS1. Gen KISS1R. Reproducción humana. Fisiología reproductiva. Mecanismos moleculares.*

Introduction

One essential quality of all living creatures required to continue life on Earth is reproduction. In addition to trying to adapt to and live in their surroundings, organisms need to create new ones to avoid going extinct[1]. Reproductive endocrinology involves complex signaling networks and feedback mechanisms to regulate reproductive functions in animals. Among these, the *KISS1* gene and its receptor *KISS1R* (*GPR54*) have emerged as key players[2].

Kisspeptin is a peptide hormone encoded by the *KISS1* gene. Many investigations[3-5] have proven kisspeptin's important functions in the regulation of various elements of reproduction. Such important regulations include the regulation of the hypothalamic-pituitary-gonadal (HPG)[6], upstream control over gonadotropin-releasing hormone (GnRH) neurons[7-9], the regulation of reproductive events such as onset of puberty, sexual maturation, and fertility and ovulation, primarily through the tight control of GnRH neurons[10,11].

Over the years, the *KISS1-KISS1R* system has been described as possessing a 'master' gene regulatory role in reproductive functions, especially through hormonal control[11-14].

Therefore, this review aims to provide a comprehensive analysis of the *KISS1-KISS1R* system, focusing on its sex-based functional differences in various animal species. By examining the distinct roles of the *KISS1-KISS1R* system in male and female reproductive endocrinology, we aim to determine whether its influence is sufficiently significant to warrant the title of "master regulator". The review will highlight the system's involvement in sexual differentiation and regulation of various reproductive functions and events.

Methods

This review adopted a traditional narrative approach with reference to the PRISMA 2020 guidelines to enhance transparency in article selection, data organization, and synthesis, even though it does not qualify as a systematic review. A comprehensive literature search was conducted across four major academic databases – PubMed, ScienceDirect, Web of Science, and Google Scholar – covering studies published in English up to March 2025. The search strategy included the use of Boolean operators to combine relevant keywords such as "kisspeptin," "*KISS1R*," "*KISS1R*," "GnRH," "hypothalamic-pituitary-gonadal axis," "reproductive endocrinology," "spermatogenesis," "folliculogenesis," "oocyte maturation," "ovulation," "pregnancy," "lactation," "infertility," and "clinical applications of kisspeptin."

Articles were selected based on their relevance to the physiological, molecular, and clinical aspects of the kisspeptin signaling system in reproductive function. Peer-reviewed original research, reviews, and clinical studies involving mammalian or human models were included, provided they were published in English and addressed the objectives of the review. Studies were excluded if they were non-English, lacked accessible full texts, or were non-peer-reviewed commentaries or editorials that did not include primary data or substantial theoretical analysis.

After the initial search, duplicate records were removed, followed by title and abstract screening to identify studies that met the inclusion criteria. Full texts of the remaining articles were then assessed to ensure relevance and quality. The final body of literature included over 90 articles that were thematically analyzed and synthesized.

The reviewed literature was organized and discussed according to key thematic areas, including the anatomical and molecular characteristics of the *KISSI1-KISS1R* system, its physiological roles in male and female reproductive function, its influence beyond reproduction – particularly in metabolic regulation and behavior – and its emerging clinical applications. The narrative approach allowed for critical integration of diverse

findings across experimental and clinical contexts, providing a comprehensive synthesis of the present state of knowledge while identifying knowledge gaps and future research directions.

Characteristics of the KISS1-KISS1R system

The *KISS1-KISS1R* system, comprising the *KISS1* gene and its receptor *KISS1R* (also known as *GPR54*), plays a central role in the regulation of reproductive endocrinology. The system's significance lies in its ability to modulate the HPG axis, influencing processes such as puberty, fertility, and overall reproductive health[6].

MOLECULAR STRUCTURE OF KISS1 GENE AND RECEPTOR

The *KISS1* gene encodes a peptide known as kisspeptin, which is a member of the RFamide family of neuropeptides. Kisspeptin exists in several forms, with the most studied being kisspeptin-54, kisspeptin-14, kisspeptin-13, and kisspeptin-10, named according to the number of amino acids they contain. The processing of the full-length kisspeptin-54 into shorter forms is a critical step in its biological activity[15,16]. All kisspeptins have the same affinity for their respective receptors[17].

Furthermore, the *KISS1R* receptor is a G protein-coupled receptor that mediates the effects of kisspeptin. It is encoded by the *GPR54* gene and is primarily expressed in GnRH neurons in the hypothalamus, although it is also found in other tissues, including the placenta and liver[16,17]. Upon binding to kisspeptin, *KISS1R* activates intracellular signaling pathways that result in the release of GnRH, thereby influencing downstream reproductive functions.

There are notable differences in the expression and function of *KISS1-KISS1R* between males and females. For instance, in females, KISS1 neurons are densely located in the anteroventral periventricular nucleus (AVPV), which is critical for the pre-ovulatory luteinizing hormone (LH) surge, while in males, these neurons are primarily located in the arcuate nucleus (ARC), reflecting their role in tonic GnRH secretion[18].

Mechanism of action

Kisspeptin binds to the *GPR54/KISS1R* receptor, activating Gq/11protein, which then activates the phospholipase-C (PLC) enzyme. PLC hydrolyses phosphatidylinositol bisphosphate to generate diacylglycerol (DAG) and inositol trisphosphate (IP_3). DAG activates protein kinase C (PKC) to regulate gene expression, while (IP_3) raises the concentration of Ca^{2+} by stimulating its release from the endoplasmic reticulum. GnRH neurons get depolarized due to the rise in Ca^{2+} causing the potassium channels to close preventing the outflow of potassium ions, and the cation transient receptor potential channels to open leading to a further influx of Ca^{2+} into the cell (Fig. 1). As a result, hormones are secreted by GnRH neurons[5]. Kisspeptin stimulates the extracellular signal-regulated kinase and mitogen-activated protein kinase (MAPK) pathways through PKC, which in turn increases apoptosis and decreases cell proliferation and metastasis[19].

Kisspeptin in the hypothalamus

The hypothalamus is a crucial brain region responsible for maintaining homeostasis and regulating various endocrine functions, including reproduction. Kisspeptin neurons in the hypothalamus are integral to the control of GnRH secretion. These neurons provide direct stimulatory input to GnRH neurons, and the activation of GnRH neurons by kisspeptin triggers the release of gonadotropins (LH and FSH) from the anterior pituitary, which in turn regulate gonadal function[20].

Kisspeptin is a critical neuropeptide that plays a vital role in regulating the HPG axis, thereby influencing reproductive function, Kisspeptin receptor (*KISS1R*) is highly expressed in the hypothalamus, particularly in regions such as the ARC and the AVPV[21].

Regulation and feedback mechanisms

The *KISS1-KISS1R* system is involved in both positive and negative feedback loops that regulate GnRH secretion. In females, the system mediates the estrogen-induced LH surge (positive feedback) that triggers ovulation, as well as the suppression of GnRH during the luteal phase (negative feedback) to prevent pre-mature ovulation. In males, KISS1 neurons regulate the negative feedback of testosterone on GnRH secretion, ensuring the proper balance of reproductive hormones[22].

Kisspeptin and puberty

Puberty begins with the strengthening of excitatory signals and the weakening of inhibitory indications over GnRH neurons, resulting in a continual rise in pulsatile GnRH production from the hypothalamus. Increased

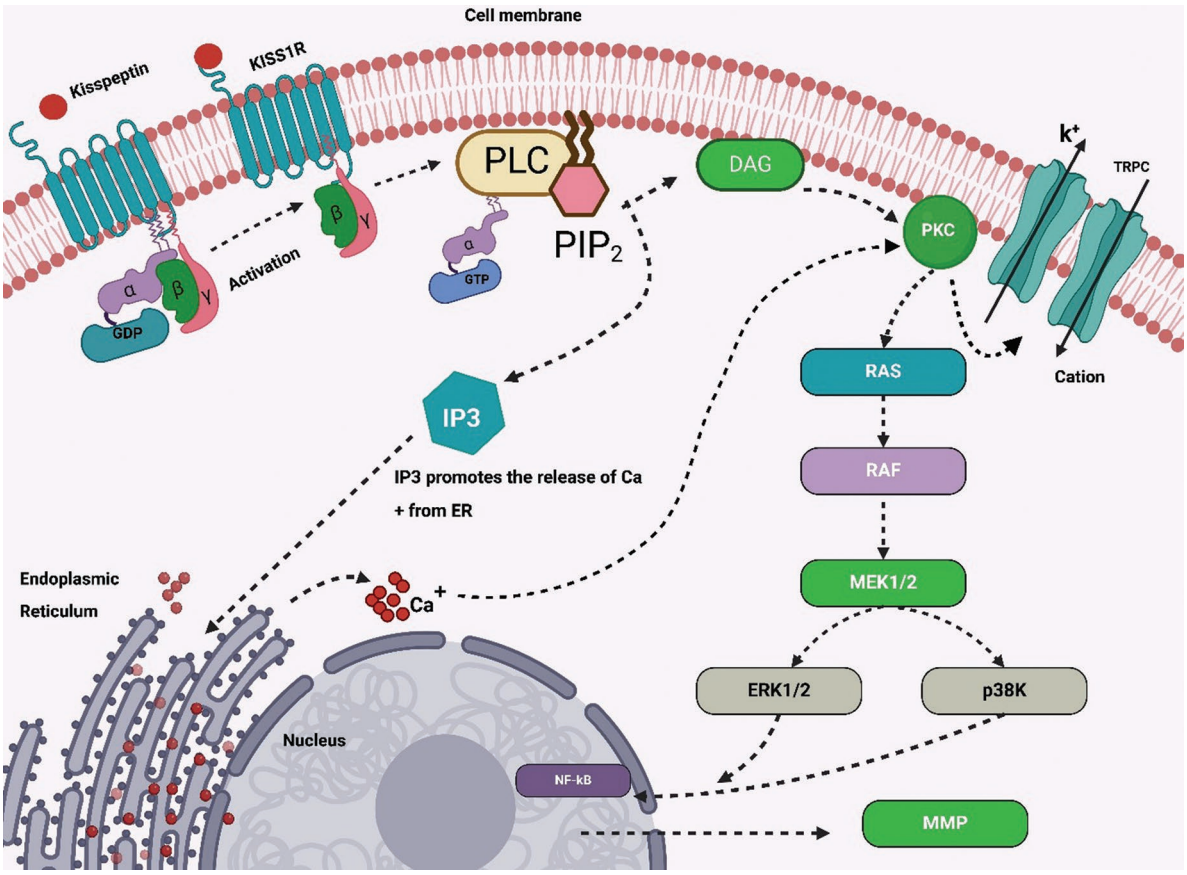

Figure 1. Intracellular signaling cascade activated by Kisspeptin Binding to the *KISS1R* receptor. This figure depicts the signaling cascade initiated by the binding of kisspeptin to the *KISS1R (GPR54)* receptor. Upon kisspeptin activation, the *KISS1R* receptor activates G-proteins, leading to the activation of phospholipase C (PLC). PLC catalyzes the breakdown of PIP_2 into inositol trisphosphate (IP_3) and diacylglycerol (DAG), with IP_3 facilitating the release of calcium ions (Ca^{2+}) from the endoplasmic reticulum (ER) into the cytosol. This increase in intracellular calcium activates protein kinase C (PKC) and the transient receptor potential canonical (TRPC) channels, which contribute to further calcium influx. The signaling cascade also involves the RAS-RAF-MEK1/2-ERK1/2 pathway, which regulates downstream gene expression through NF-κB and matrix metalloproteinase (MMP) activation. These signaling events play a crucial role in regulating gonadotropin-releasing hormone secretion, reproductive function, and cellular processes, as highlighted in the review.

GnRH pulse activates downstream components, resulting in increased gonadotropins and sex hormones, gametogenesis, secondary sex characteristics, and fast development, all of which contribute to fertility[23]. Although kisspeptin is vital for pubertal development in both males and females, there are notable differences in its function and regulation between the sexes.

In females, kisspeptin is integral to the initiation of puberty and the regulation of the menstrual cycle. The hormone exerts its effects by acting on GnRH neurons to initiate the pre-ovulatory surge of GnRH, which is critical for the onset of ovulation[24]. Kisspeptin neurons in the AVPV and the ARC of the hypothalamus are particularly important in females. The AVPV kisspeptin neurons are implicated in the positive feedback mechanism of estrogen, which induces the LH surge necessary for ovulation[25].

In males, kisspeptin is essential for the activation of the HPG axis during puberty, leading to increased testosterone production and spermatogenesis (Fig. 2). Unlike in females, the regulation of kisspeptin in males does not involve a pre-ovulatory surge but is crucial for maintaining steady-state levels of GnRH and LH secretion necessary for testicular function[10]. Kisspeptin neurons in the ARC play a more prominent role in males,

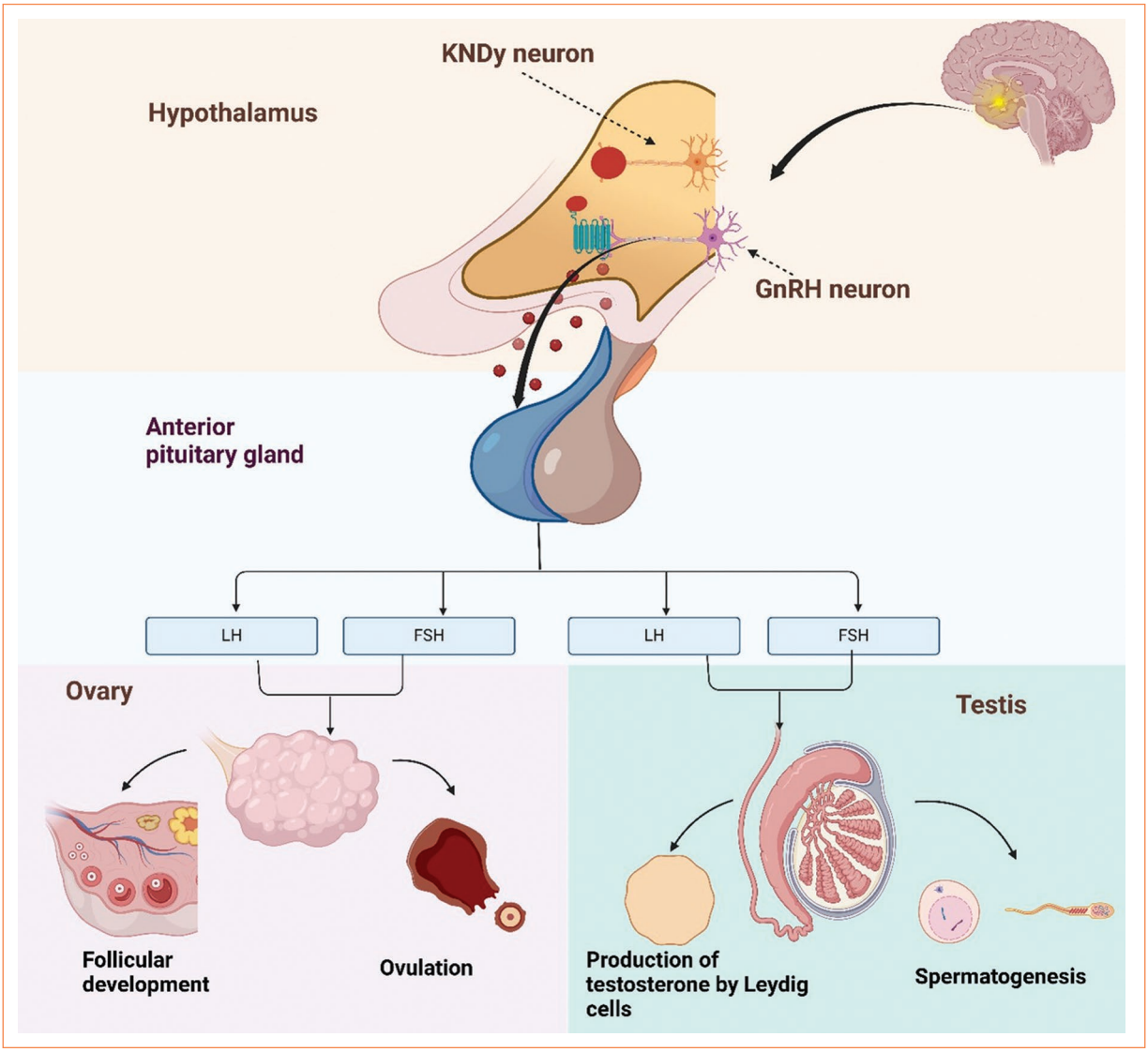

Figure 2. Regulation of the hypothalamic-pituitary-gonadal axis by the *KISS1-KISS1R* system. This figure illustrates the regulatory cascade of the hypothalamic-pituitary-gonadal (HPG) axis mediated by the *KISS1-KISS1R* system. In females, kisspeptin is primarily produced by neurons in the anteroventral periventricular nucleus (AVPV) of the hypothalamus. Here, kisspeptin stimulates gonadotropin-releasing hormone (GnRH) neurons, promoting the release of gonadotropins (LH and FSH) from the anterior pituitary, which subsequently trigger follicular development and ovulation. In males, kisspeptin is mainly synthesized by neurons in the arcuate nucleus (ARC). Kisspeptin in this region regulates the tonic secretion of GnRH, leading to continuous gonadotropin release that stimulates testosterone production by Leydig cells in the testes and supports spermatogenesis. Both in females and males, the interaction of kisspeptin with its receptor, *KISS1R (GPR54)*, in the hypothalamus leads to downstream signaling events, resulting in the activation of the HPG axis and gonadal function.

where they are involved in the negative feedback regulation of gonadotropin secretion by testosterone[26].

The sexually dimorphic nature of kisspeptin's role in puberty is influenced by sex steroids, such as estrogen and testosterone, which differentially regulate kisspeptin expression and action in the hypothalamus[27].

The administration of kisspeptin has been investigated as a potential strategy to enhance pubertal development, particularly in cases of delayed or disrupted puberty. Studies in both male and female animal models have shown that exogenous kisspeptin can stimulate the HPG axis, leading to the onset of puberty.

In female models, kisspeptin administration has been shown to advance the timing of puberty by inducing the early release of GnRH and subsequent increases in LH and FSH levels, which promote ovarian development and estrogen production. This acceleration of puberty is associated with earlier onset of estrous cycles and ovulation[28]. In addition, kisspeptin treatment has been observed to restore reproductive function in female models with impaired kisspeptin signaling, indicating its therapeutic potential[29].

In male models, kisspeptin administration has similarly been shown to advance the onset of puberty by stimulating GnRH release and increasing LH and FSH secretion. This leads to enhanced testosterone production and spermatogenesis[12]. The continuous or pulsatile administration of kisspeptin can effectively mimic the natural activation of the HPG axis, resulting in the advancement of pubertal milestones, such as testicular enlargement and increased secondary sexual characteristics[30].

Puberty cannot occur without normal Kisspeptin-receptor contact, as demonstrated by inactivating mutations of the *GPR54* gene in hypogonadotropic hypogonadism (HH) patients[31,32]. Endogenous kisspeptin rhythmicity and sensitivity increase with puberty; in primates and rats, both the number of KISS1 neurons and the amount of KISS1 mRNA have been found to rise during the juvenile-pubertal transition[33-35].

Kisspeptin in male reproduction

KISS1 and *KISS1R* in testis and spermatozoa

Spermatogenesis is a complex process modulated step-by-step by the autocrine, paracrine, and endocrine routes. It needs the coordination between germ cell proliferation and death, meiotic division and differentiation events, and the key contribution of Leydig cells in the interstitium to produce sex-steroids, and Sertoli cells in the seminiferous tubules to provide structural and nourishment support to developing germ cells[36]. The kisspeptin system has been characterized in the testis of mammalian and non-mammalian vertebrates, revealing possible roles in the autocrine and paracrine intra-testicular communications, steroid biosynthesis, spermatogenesis progression, and sperm functions, but also species-specific differences in localization and possible functions[37-39]. Kisspeptin, but not GnRH, has been detected in human plasma and measured in different health conditions[40]. In males, circulating kisspeptin levels change in fertility status, being significantly higher in fertile than in infertile men[41]. Some hypogonadotropic HH patients have high levels of kisspeptin in the plasma, but, after GnRH replacement therapy, circulating kisspeptin levels decrease as a consequence of the restored sex-steroid feedback mechanisms at hypothalamic levels[42]. However, gonadotropin stimulation is not always able to rescue testosterone biosynthesis and spermatogenesis in clinical cases of *KISS1R* inactivating mutations[43,44], suggesting the need for testicular *KISS1R* signaling for steroidogenesis. Similarly, the specific reactivation of the *KISS1R* gene in the GnRH-secreting neuron of *KISS1R* knockout mice does not restore spermatogenesis, further confirming the need for the intratesticular kisspeptin signal for successful spermatogenesis[45]. By contrast, testosterone replacement in KISS knockout mice that exhibit HH restores plasma and intratesticular testosterone levels and sustains spermatogenesis until the production of spermatozoa capable of fertilizing eggs *in vitro*, but treated mice failed to impregnate females[46]. The administration of kisspeptin usually promotes spermatogenesis in intact animal models[47-49]. Post-natal testis development and Leydig cell maturation require kisspeptin signaling, and synergistic effects involving both the hypothalamic and LH-dependent intratesticular production of kisspeptin have been suggested in rodents[50].

Kisspeptin in female reproduction

The role of kisspeptin in follicular development

Kisspeptin levels increase from the early follicular to the pre-ovulatory phase[40] in females. In the process of follicular development, kisspeptin affects primary and secondary follicle recruitment by reducing the FSH receptor (FSHR) expression. In both 6 and 10-month-old rats, local administration of kisspeptin into the ovary reduced the number of total antral follicles (including atretic follicles) and the use of kisspeptin receptor antagonist p234 played the opposite role[51]. In an *in vitro* experiment, kisspeptin acted as a functional antagonist by preventing the increase in FSHR expression produced by Isoproterenol, a β-adrenergic agonist. Besides, kisspeptin can upregulate the level of serum anti-Müllerian hormone (AMH), which is a vital dimeric glycoprotein in the regulation of follicle development. Produced by pre-antral and small antral follicles, AMH exerts its regulatory role by attenuating primordial follicle recruitment and changing the sensitivity of follicles to FSH[52,53]. The study found that serum AMH levels increased after local administration of kisspeptin and

decreased after the use of p234 in 6 and 10-month-old rats. To sum up, kisspeptin may negatively affect the development of pre-antral follicles by upregulating AMH and downregulating the expression of FSHR in the ovary.

The role of kisspeptin in oocyte maturation

It is well known that the pre-ovulatory LH surge triggers the resumption of meiosis and the progression to metaphase II during each reproductive cycle[54]. Besides, the direct effect of kisspeptin on oocyte maturation has been studied in porcine cumulus-oocyte complexes (COCs). Adding kisspeptin to porcine COCs *in vitro* promotes oocyte maturation, suggesting kisspeptin acts on oocytes directly[55]. The mechanisms may include upregulating the expression of C-MOS, growth differentiation factor 9 (GDF 9), and bone morphogenetic protein 15 (BMP 15)[56]. C-MOS plays a stimulating role in various processes during oocyte maturation, including the meiosis process, normal spindle and chromosome formation, and reactivation of purified maturation-promoting factor after first meiosis. Furthermore, GDF 9 and BMP 15 take part in regulating follicle development, oocyte maturation, ovulation, luteinization, and other physiological processes[56,57]. It has been found that cumulus granulosa cells (GCs) play a vital role in regulating oocyte maturation. Several researchers have observed a remarkable expression of kisspeptin in gonadotropin-treated GCs, while *KISS1R* in oocytes, suggesting that GC-derived Kisspeptin may have a direct function on oocytes *KISS1R* to modulate oocyte maturation through a MAPK signaling pathway[58-60]. The kisspeptin expressed in GCs is estrogen receptor beta (ERβ) dependent since the expression of kisspeptin in GCs is absent in ERβ knockout rat ovaries. Consistent with the findings above, the administration of kisspeptin can increase the maturity of oocytes without cumulus cells in both wild-type and ERβ knockout rats[58]. Therefore, kisspeptin may have a persistent and direct effect on oocytes in an autocrine and paracrine manner.

The role of kisspeptin in ovulation

Ovulation is a complicated process described as the follicle rupture and oocyte release, which is mediated by the LH surge and is regulated by a series of specific genes[61]. At the end of the follicular phase, high levels of estrogen act on AVPV kisspeptin neurons, promoting the release of kisspeptin, which then causes the cascade of GnRH surge, LH peak, and ovulation[62]. The functions of the LH peak are achieved by upregulating the expression of COX-2 and producing prostaglandin, which are essential for follicular rupture and ovulation[63]. It has been confirmed that peripheral kisspeptin administration induces ovulation in many species, such as rats and ewes[64]. The effect of kisspeptin on ovulation is mainly achieved by increasing the levels of LH and FSH. Subcutaneous administration of kisspeptin markedly elevated plasma FSH and LH levels in 25-day-old female rats[65]. In humans, the LH pulses increased immediately after an administration of kisspeptin-10[40]. Kisspeptin-54 induced ovulation in mice by stimulating precisely timed endogenous LH release of consistent amplitude and duration[66]. Both the expression of ovarian KISS1 mRNA and the ovulation efficiency in rats could be reduced by the administration of a COX-2 inhibitor or a COX non-selective inhibitor, indicating that the upregulation of COX-2 may act on the expression levels of kisspeptin to induce the LH peak[67]. The role of ovarian kisspeptin in ovulation may not be indispensable because, in *KISS1R* knockout mice, standard gonadotropin priming could induce ovulation[12], indicating that the ovarian kisspeptin signaling is not necessary for ovulation. However, although the oocyte quality between neuron-specific KISS1 and *KISS1R* knockout mice and wild-type mice shows little difference, the knockout mice presented fewer ovulated oocytes and corpora lutea. This suggests the GnRH plus gonadotropin stimulation is not sufficient to reverse the loss of function due to *KISS1R* knockout[68].

The role of kisspeptin in pregnancy and lactation

Kisspeptin concentrations in human plasma increased dramatically throughout pregnancy, with the placenta producing the majority of it. Histochemical investigation revealed that KISS1 mRNA is localized in syncytiotrophoblast; these findings imply that kisspeptin may play a function in regulating trophoblast invasion. The greatest levels of KISS1 and *KISS1R* mRNAs in trophoblast cells correspond to maximal trophoblast invasion, which should be appropriately controlled.

Kisspeptin was reported to suppress the metastasis in cancer cells, and *KISS1* expression levels were revealed to be lower in metastatic compared with non-metastatic cancer tissue[16,69]. Trophoblasts are cells that are important for the growth and attachment of the placenta to the uterus. Trophoblast invasion resembles tumor metastasis[70] as the invading

trophoblasts follow a similar molecular mechanism for migration and invasion as tumor cells. The discovery of high levels of endogenous kisspeptin and *KISS1R* in placental trophoblast[71,72], suggests its direct involvement in inhibiting cellular invasion, migration, and angiogenesis, thereby preventing excessive invasion of the endometrium by trophoblast cell[73].

Recent research has demonstrated that central Kisspeptin 10 injection stimulates oxytocin neurons during the end of pregnancy and throughout lactation, indicating that Kisspeptin-induced oxytocin release is essential for parturition and lactation. Increased plasma Kisspeptin during pregnancy may thereby enhance oxytocin release; yet oxytocin receptor expression and sensitivity remain low before childbirth[74].

However, studies in mice have revealed that prolactin treatment significantly decreased Kisspeptin expression in the hypothalamus, reducing GnRH release. Again, utilizing bromocriptine as a prolactin suppressor resulted in significantly enhanced KISS1 mRNA expression in the rostral periventricular region of the third ventricle (RP3V) in mice. Furthermore, during breastfeeding, rats revealed lower expression of KISS1 mRNA in the hypothalamus and LH secretion, resulting in the shutdown of the estrous cycle. Indeed, in virtually all animals, breastfeeding generates a period of infertility that allows for healthy offspring development and survival, and proper regulation of Kisspeptin expression contributes to lactational anovulation[75,76].

The role of kisspeptin beyond reproduction

Recent studies have shown that kisspeptin may also play a role in the regulation of energy balance and metabolism[77]. Report an altered metabolic phenotype in *KISS1R* knockout adult female mice. These mice showed significantly increased body weights and adiposity, impaired glucose regulation, and reduced energy expenditure from 10 weeks of age. Studies have shown that chronic intracerebroventricular kisspeptin treatment from post-natal day decreased body weight at day 60 in female rats[78]. This link suggests that kisspeptin acts as a mediator between metabolic status and reproductive health.

Kisspeptin has been implicated in the regulation of reproductive behaviors. It influences sexual motivation and mating behavior in animals, with evidence suggesting that it may modulate the neural circuits involved in these behaviours[79]. This role extends the influence of the *KISS1-KISS1R* system beyond purely physiological aspects to encompass behavioral regulation as well.

The involvement of the *KISS1-KISS1R* system in memory and learning processes was suggested by the wide expression of *KISS1R* in the learning and memory-associated brain regions, including the dentate gyrus of the hippocampus and the cortical and medial nucleus of the amygdala[80]. It has been reported that intracerebroventricular administration of kisspeptin-13, during a passive avoidance paradigm, enhances learning and stabilizes memory[81].

The potential role kisspeptin in clinical application

In recent years, many attempts have been made to explore the possibility of kisspeptin as a new diagnostic marker or therapeutic option. In humans, the plasma level of kisspeptin (kisspeptin-54) increases dramatically throughout pregnancy, making it possible to detect early pregnancy by measuring plasma kisspeptin concentrations[82]. Furthermore, because kisspeptin is produced by trophoblasts and trophoblast invasion is underway 5 days after blastocyst transplantation, plasma kisspeptin concentrations during the peri-implantation period may reflect the early developmental events associated with pregnancy outcome[82]. In a comparative study[83], measured serum kisspeptin in 20 women with 6-10 weeks of intrauterine pregnancy (IUP) and 20 women who suffered spontaneous abortion (SAB) at a similar time. They found the median serum kisspeptin levels were significantly higher in IUP women (1.50 ng/mL) than in SAB women (0.20 ng/mL), indicating that kisspeptin is detectable in serum in early pregnancy and can discriminate SAB from IUP[83]. Girls with central precocious puberty (CPP) had higher serum kisspeptin levels compared with healthy girls[84,85]. However, serum kisspeptin levels are not able to become a single diagnostic tool because the evident overlap limits its use, while it may still be useful as an adjunctive tool in the diagnosis of CPP. As for therapeutic options, kisspeptin is found to have the potential to stimulate oocyte maturation and induce ovulation in infertile women. In 2014, a clinical study found that a single administration of kisspeptin-54 induced female egg maturation in women who accepted *in vitro* fertilization[86] suggesting its potential application in treating women with infertility. Kisspeptin and its agonist are also regarded as potential therapeutic options for some reproductive diseases. In a clinical study, repeated administration of kp-54 successfully induced ovulation

in two out of seven women with polycystic ovary syndrome (PCOS)[87]. Abbara and colleagues[88] compared the therapeutic effect of nanopeptide *KISS1R* agonist MT-602 and kisspeptin 54 in PCOS women and found both MVT-602 and kp54 induced an LH peak with similar amplitude. Recent studies also reported the application of kisspeptin as a future therapeutic option in the treatment of hyperprolactinemia, a condition characterized by elevated levels of prolactin, which inhibits GnRH, LH, and FSH secretion, and could cause irregular menstruation and infertility[89]. The administration of kisspeptin successfully caused LH pulses through stimulating GnRH in women with hyperprolactinemia[90]. In another study, the use of kisspeptin induced recovery of gonadotropin secretion[89]. In addition, based on the fact that a high dose of kisspeptin leads to desensitization of the HPG axis, kisspeptin may be applied in the treatment of sex hormone-dependent malignancies. For example, prostate cancer is a kind of androgen-dependent malignancy, and the present primary treatment is androgen deprivation therapy[91]. Two animal studies have confirmed that chronic administration of the kisspeptin analog, TAK-448 caused a stronger inhibiting effect on the HPG axis than GnRH analog and suppressed testosterone and LH release, indicating its great anti-tumor growth potential[92,93].

Conclusion

The *KISS1-KISS1R* system is a pivotal regulator of reproductive endocrinology, with profound implications for both male and female reproductive health. Its role in the activation of the HPG axis, particularly in the initiation of puberty, regulation of the menstrual cycle, and maintenance of fertility, underscores its central position in the reproductive hormonal hierarchy. The sex-specific expression and function of *KISS1-KISS1R* highlight the nuanced and essential roles it plays in coordinating reproductive processes in both sexes. Furthermore, the system's involvement extends beyond reproduction, influencing energy balance, metabolism, and reproductive behaviors, which points to its broader significance. When compared to other reproductive hormones, kisspeptin stands out due to its upstream regulatory role, controlling the release of GnRH and consequently the entire cascade of reproductive hormones. This unique position justifies the characterization of kisspeptin as the master regulator of reproductive endocrinology.

Future research into the *KISS1-KISS1R* system's mechanisms and potential clinical applications could open new avenues for the treatment of reproductive disorders, enhancing our understanding of this complex and vital regulatory network. The evidence supports the notion that the *KISS1-KISS1R* system is indeed the "master regulator" of reproductive endocrinology, making it a key focus for ongoing and future studies in reproductive biology.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that ChatGPT 4.0 was used in this work, and it was utilized only for translation purposes from English to Spanish. No other AI tools were used.

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