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Review Article

The role of kisspeptin neuropeptide in controlling reproduction

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Abstract

The pulsatile release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus serves as the ultimate output signal for the regulation of reproductive processes, which integrate a number of elements from both the internal and external environment. A potent endogenous secretagogue of GnRH, kisspeptin, is produced by hypothalamic neurons. Kisspeptin has physiological relevance and a variety of reproductive functions. It controls both the pulsatile GnRH secretion that drives folliculogenesis, spermatogenesis, and steroidogenesis as well as the GnRH surge that causes ovulation in females. It plays a crucial role in the central regulation of the timing of puberty onset and reproduction in animals. Kisspeptin and related substances could therefore be valuable for the development of novel strategies for the management of fertility in farm animals and are now universally recognized as a key player in the control of critical aspects of reproductive development and function from sexual differentiation to regulation of GnRH /gonadotropin secretion.

Keywords: GnRH, Hypothalamus, Puberty, Reproduction

Highlights

- Kisspeptin can play a role to attain early puberty in female.
- Kisspeptin can be used as an alternative to gonadotropins for the synchronization of oestrus and ovulation.

INTRODUCTION

Neurons produce and release small proteins known as neuropeptides through the regulated secretory route, where they operate on neural substrates (Li and Kim, 2008). The largest family of signalling molecules in the brain, neuropeptides have a role in a variety of physiological processes. Nutrition and the availability of stored energy reserves are the two factors that control fertility, but the cellular and molecular mechanisms connecting energy reserves and reproduction are not fully known.

Neuropeptides like galanin-like peptide (GALP), Neuropeptide Y (NPY), products of proopiomelanocortin (POMC), such as -MSH and -endorphin, and kisspeptin have a role in controlling reproduction (Russo, 2017). First, the hypothalamic arcuate nucleus, a crucial area for the control of both metabolism and reproduction, is linked to all of the neurons that express these neuropeptides; secondly, metabolic hormones like leptin and insulin all have these neuropeptides as targets for controlling their levels (Harter *et al*., 2018). Third, these neuropeptides have an impact on luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) secretion as well as on feeding and metabolism (Crown *et al*., 2007).

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are gonadotropins that the brain uses to control the gonads, are stimulated by the action of GnRH on the adenohypophysis (Marques *et al*., 2022). In response to gonadotropins, the gonad releases steroid hormones such as oestrogen and progesterone in females and androgens in males, which subsequently give feedback to the hypothalamus to alter GnRH output. This circuit called the hypothalamic-pituitary-gonad (HPG) axis, regulates the reproductive system (Acevedo Rodriguez *et al*., 2018).

There are two distinct forms of GnRH secretion: the preovulatory gonadotropin surge mode, which results in ovulation in females in response to estrogen-positive feedback. The tonic gonadotropin secretion's pulsatile mode, which promotes steroidogenesis, spermatogenesis, and folliculogenesis (Matsuda *et al*., 2019). There are still a number of critical issues that need to be resolved even if the aforementioned scenario has been regarded as the basic principle of the regulation of reproduction (Sethi *et al*., 2021).

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For example, how are the two modes of GnRH secretion generated, and how are steroid hormone signals transmitted to GnRH neurons that lack estrogen receptor alpha (ERa) (Marques *et al*., 2022) mediating the feedback action of estradiol (E2) on GnRH secretion? Kisspeptin, a recently identified peptide, offers crucial hints for resolving these enduring concerns and has ushered in an exciting new age in reproductive endocrinology (Nejad *et al*., 2017).

Kisspeptin: A neuropeptide

A class of structurally similar peptides known as kisspeptin is produced by the KISS1/Kiss1 gene and functions by binding to and then activating the G protein-coupled receptor GPR54. The KISS1 gene's transcript was discovered to be selectively repressed in melanoma cell lines with strong metastatic capability in 1996, making it the first component of the system to be described (Lee *et al*., 1996). Due to its partial similarity with the transmembrane domains of galanin receptors (and being unrelated to Kiss1), GPR54 was cloned in the rat brain three years after it was discovered to be an orphan receptor (Lee *et al*., 1999). Kisspeptins are a collection of structurally similar peptides that were discovered in 2001 to be the major peptide products of the Kiss1 gene. These peptides are created when various proteases digest a common precursor in various ways. The primary peptide of the family, kisspeptin-54, has been given the name "metastin" because of its ability to prevent tumor invasion. Kisspeptin-10, also known as Kp-10, a 10-amino-acid segment at the C terminus, was shown to be adequate for receptor activation. Due to their shared Arg-Phe-NH2 motif at the C-terminus, the KPs, which are encoded by the KiSS-1 gene, belong to a class of peptide hormones known as RF-amides (Hu *et al*., 2022). It was also shown that all known kisspeptins can bind to GPR54, which was subsequently designated as the cognate receptor of Kiss1-derived peptides. It was also reported that human idiopathic hypogonadotropic hypogonadism was linked to inactivating mutations of the kisspeptin receptor gene (GPR54) (de Roux *et al*., 2003; Seminara *et al*., 2003). This human genetic discovery received experimental support with the development of GPR54 null mice, which exhibit reduced gonadal growth, low amounts of gonadotropins and steroid hormones, and are incapable of going through puberty (Seminara *et al*., 2003). These findings identified kisspeptin/GPR54 signaling as a novel player in the HPG axis, and as a result, over the past several years, rigorous and extensive research on kisspeptin has been conducted.

Despite playing a crucial role in both the positive (Wintermantel *et al*., 2006) and negative (Dorling *et al*., 2003) feedback effects of E2 on GnRH production, GnRH neurons do not express ERa (Shaw *et al*., 2010). As a result, another set of neurons must operate as a mediator for the influence of E2 activity on GnRH neurons. The fact that practically all kisspeptin neurons express ERa in the ARC and around half do so in the POA in sheep makes them one of the many groups of neurons that stand out (Franceschini *et al*., 2006). Furthermore, according to Smith *et al*. (2007), the progesterone receptor in the ovine ARC is present in about 90% of kisspeptin neurons. In the preoptic region (POA) and medial basal hypothalamus (MBH), around 40% to 50% of GnRH neurons in sheep receive kisspeptin fibers immediately opposite to their cell bodies (Smith *et al*., 2008). This proportion increases to about 100% in the MBH during the breeding season but not in the POA (Smith *et al*., 2008). Such apposition is only found in a tiny subset of the GnRH neurons in the male goats' POA. Kiss2 has been identified as a second Kiss-like gene in fish and other non-mammalian species, despite the fact that placental mammals have only one Kiss1 gene in their genomes (Felip *et al*., 2009). This gene encodes a decapeptide that differs greatly from mammalian Kp-10 (encoded by Kiss1). But it was shown that in animals like the teleost sea bass, this Kiss2-derived decapeptide was more potent than Kp-10 in triggering gonadotropin secretion.

MOA of kisspeptin

The activation of G protein-activated phospholipase C (PLC) in the binding of Kiss1r by Kiss1 peptide suggests a Gq/11-mediated signalling pathway (Kotani *et al*., 2001; Muir *et al*., 2001; Stafford *et al*., 2002; Constantin *et al*., 2009).

Inositol triphosphate (IP3) and diacylglycerol (DAG), two intracellular second messengers produced as a result of PLC activation, respectively mediate the release of intracellular Ca2+ and the activation of protein kinase C (Stafford *et al*., 2002; Constantin *et al*., 2009). Kisspeptin is thought to stimulate the secretion of GnRH through the activation of transient receptor potential canonical (TRPC)-like channels and the inhibition of inwardly rectifying potassium channels (Zhang *et al*., 2008), both of which may be mediated by DAG and/or Ca2+ (Fig. 1).

Where kisspeptin neurons located?

The hypothalamic arcuate nucleus contains the majority of kisspeptin neurons, particularly in its caudal region that extends to the pre-mammillary nucleus.

This is well protected in sheep (Estrada *et al*., 2006), goats (Okamura *et al*., 2013), cattle (Hassaneen *et al*., 2016), horses (Magee *et al*., 2009) and pigs (Goodman *et al*., 2007; Lents, 2019).

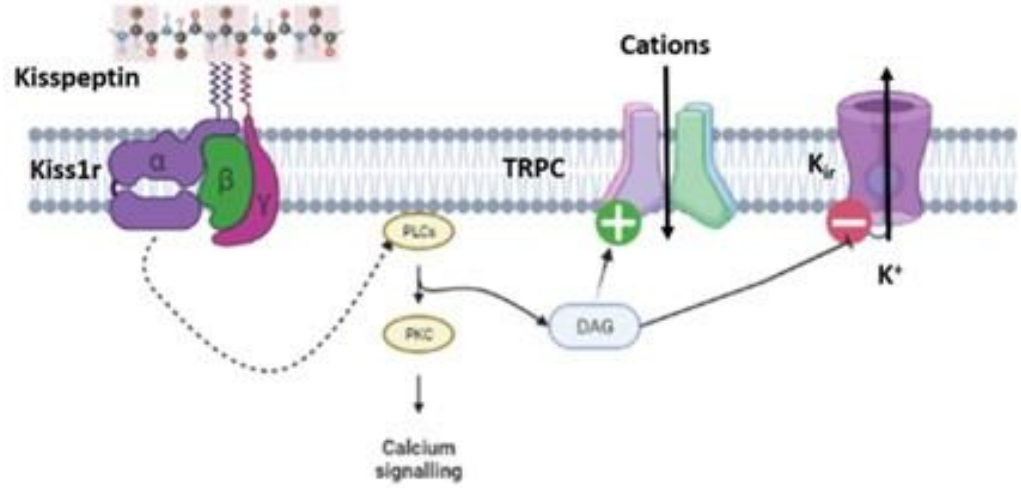

Fig. 1. Mechanism of action of kisspeptin

The medial preoptic region of sheep, goats, and calves has the second-highest number of kisspeptin cells (Estrada *et al*., 2006; Franceschini *et al*., 2006; Goodman *et al*., 2007; Hassaneen *et al*., 2016).

In contrast, horses (McGrath *et al*., 2016) do not seem to have any kisspeptin neurons in the preoptic region. In addition, several cells are found in the dorsomedial nucleus and a few in the ventromedial nucleus of sheep, horses and cattle (Franceschini *et al*., 2006; Hassaneen *et al*., 2016).

The rostral population of kisspeptin neurons in pigs is situated in the periventricular nucleus as opposed to the preoptic region (Lents, 2019). Nearly all kisspeptin neurons in the arcuate nucleus coexpress neurokinin B and dynorphin (Goodman *et al*., 2007). They are known as KNDy (Kisspeptin/Neurokinin B/Dynorphin) neurons as a result of this co-localization (Hassaneen *et al*., 2016). KNDy neurons have only been found in the arcuate population of kisspeptin neurons. In sheep, around 90% of KNDy neurons express the kappa opioid receptor, which is the receptor for dynorphin, while the majority of KNDy neurons express the NK3 receptor, the receptor for neurokinin B (Li *et al*., 2020). Thus, both NK3 and kappa opioid receptors are expressed by KNDy neurons. Kisspeptin neurons, on the other hand, lack the kisspeptin receptor (kiss1R) (Smith *et al*., 2011), demonstrating that dynorphin and neurokinin B, rather than kisspeptin, are the means of communication amongst KNDy neurons. This association seems functional since the central infusion of neurokinin B activated kisspeptin neurons in anoestrous ewes and significantly raised the proportion of kisspeptin neurons expressing the neuronal activation marker Fos.

Steroidal loop: The kisspeptin system may be involved in the two important negative and positive feedback loops of the hypothalamus pituitary-gonadal axis. Pulsatile LHRH released into the hypophyseal portal blood induces the production of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are then secreted in the peripheral circulation and stimulate the release of sex steroids from the gonads (Maeda *et al*., 2010). Gonadal sex steroids then stop LHRH from being released, completing the negative feedback loop. Sex hormones increase rather than decrease LHRH production in females, which results in the preovulatory spike in FSH and LH. As a result, the positive feedback loop is closed. Negative feedback response to sex steroids appears to be mediated by Kiss-1 neurons in the ARC/infundibular nucleus in rates (Smith *et al*., 2005, 2006; Kinoshita *et al*., 2005; Adachi *et al*., 2007), sheep (Estrada *et al*., 2006; Goodman *et al*., 2007; Smith *et al*., 2009), and primates (Rometo *et al*., 2007; Smith *et al*., 2010; Hrabovszky *et al*., 2019). On the other hand, the neural circuit that controls the positive feedback regulation is probably supplied by Kiss-1 cells in the AVPV of rodents. This result supports that the gonadal steroid level controls Kiss-1 expression in Kiss-1 neurons, expresses estrogen receptor alpha (ER), and exogenous kisspeptin can activate gonadotropin release (Clarkson *et al*., 2009).

Proteolysis: In most mammals, the kisspeptin protein, which is 52–54 amino acids long and encoded by the Kiss1 gene, is cleaved from a precursor peptide (Oakley *et al*., 2009). Kisspeptin's amino acid sequence is largely conserved among mammals (Kim *et al*., 2012; Lents, 2019). For instance, the amino acid sequences of ovine, bovine and pig kisspeptin share, respectively, 98, 91, and 77% of their amino acid sequences with that of goat

kisspeptin. Except for primates, where the C-terminal tyrosine (Y) is changed to phenylalanine (F), all of the species listed have the same C-terminal 10 residues, which constitute the minimal core sequence for maximal receptor activation (Kotani *et al*., 2001). It is common to practice examining the physiological effects of kisspeptin in vertebrates, including fish, using the commercially available kisspeptin C-terminal decapeptide Kp-10 (Kanda *et al.*, 2008).

Applications of kisspeptin

Pubertal onset: Several lines of evidence suggest that the key players in this mechanism are ARC KNDy neurons, which serve as the GnRH pulse generator, regulate pulsatile GnRH/gonadotropin secretion and hence pubertal onset in mammals including rodents (Matsui *et al.*, 2004), ruminants (Smith *et al.*, 2009) and primates (Shahab *et al.*, 2005). GnRH pulse generation is postulated to be suspended by a lack of kisspeptin secretion in mammals during the pre-pubertal period (de Roux *et al.*, 2003; Seminara *et al.*, 2003).

A pubertal rise in Kiss1 expression in rodents and kisspeptin production from the median eminence in primates was documented in earlier research. It's intriguing to notice that many animals have distinct underlying mechanisms for preventing the production and release of kisspeptin during the pre-pubertal stage. Ovariectomy rapidly stimulated gonadotropin secretion even in the pre-pubertal phase in rats and sheep, while oestrogen replacement reduced gonadotropin secretion until a normal pre-pubertal time (Takasee *et al.*, 2009; Uenoyama *et al.*, 2019). These studies indicate that oestrogen is essential for the pre-pubertal regulation of GnRH and gonadotropin production and that its inhibitory effect appears to diminish during the pubertal transition. According to Takasee *et al*. (2009), estrogen actually significantly lowers the expression of ARC Kiss1 in female rats during the pre-pubertal stage but only slightly lowers it during the post-pubertal stage. Additionally, ovariectomy raised the proportion of ARC kisspeptin-immunoreactive cells in sheep during the pre-pubertal stage but not during the post-pubertal stage (Nestor *et al.*, 2012). The traditional "gonadostat hypothesis" (Uenoyama *et al.*, 2019), which proposes that the pubertal increase in GnRH and gonadotropin secretion in rodents would be accompanied by a decrease in the sensitivity to the negative feedback action of oestrogen, is supported by the regulation of ARC Kiss1 expression by oestrogen during the pubertal transition. According to Mayer *et al.* (2010) and Dubois *et al.* (2016), kisspeptin neuron-specific ER knockout mice showed early increases in ARC Kiss1 expression and gonadotropin secretion, which caused the early onset of pubertal development. They suggested that a small amount of oestrogen from the developing ovary directly inhibits Kiss1 expression in kisspeptin neurons via the oestrogen receptor (ER). In fact, during the pre-pubertal stage in ovariectomized rats, oestrogen implantation into the ARC decreased LH pulses (Uenoyama *et al.*, 2015). Intriguingly, oestrogen implantation into the POA also reduced LH pulses in pre-pubertal ovariectomized rats, indicating that the ARC kisspeptin neurons are not the only oestrogen receptors that act as an inhibitory site to reduce Kiss1 expression and consequently, GnRH and gonadotropin secretion in rats (Uenoyama *et al*., 2015). More research is required to determine why oestrogen sensitivity declines in rats and sheep during the pubertal transition.

Synchronization: Kisspeptin, a potent secretagogue of GnRH, has been used to provide a new way of synchronizing estrus/ovulation in crossbred cows (Mondal *et al*., 2015). Estrus synchronization protocols are based mainly on GnRH and/or PGF2α or their combination thereof. Undoubtedly, the GnRH or its analogs are the top priority for this purpose. Efforts for the regulation and control of follicular dynamics using GnRH have been made in cattle (Mondal *et al.*, 2015). Ovulation synchronization using GnRH followed by Timed Artificial Insemination (TAI) has been reported to be satisfactory in terms of conception rates. Recently, kisspeptin has been reported to be a potent secretagogue of GnRH and plays an important role in the regulation of reproduction in animals (Macedo *et al.*, 2021). Kisspeptin (a product of the KiSS1 gene) acts mainly by controlling GnRH secretion in the brain. It has been found to induce preovulatory LH surges more efficiently than gonadotropins with a very low dose. Therefore, it is anticipated that administering kisspeptin in the protocol instead of GnRH may induce early ovulation and consequently an earlier development of CL (Mondal *et al*., 2022).

Kisspeptin analogs: The great majority of *in vivo* studies emphasizing the potential of targeting the Kp system used Kp10 and to a lesser extent Kp54. According to Chan *et al.* (2011) and Asami *et al.* (2012), the half-life of Kp10 in the blood of mice and humans is 55 and 34 seconds, respectively, and the half-life of Kp54 in human blood is 27.6 minutes (Dhillo *et al.*, 2005). Because of their short half-lives, prolonged intravenous infusions are necessary to produce the desired effects. If the infusion is still a viable choice for a certain therapeutic intervention in humans, it is not relevant for managing

livestock. A substance that produces the desired effect with a single intramuscular or subcutaneous injection is needed for field applications. This issue would therefore be solved by creating a synthetic kisspeptin ligand with an appropriate mode of administration and pharmacodynamic profile.

Two main approaches are possible:

1. High throughput screening for the discovery of synthetic small molecules unrelated to the original peptide and its subsequent optimization (Beltramo and Decourt, 2018).
2. Specific changes to the endogenous peptide increase its stability and resistance to breakdown (Beltramo and Decourt, 2018).

The use of small molecules to substitute for endogenous peptides has proven difficult but remains a viable option. Concerning the second approach, successful examples of half-life prolongation of short-lived endogenous peptides by molecular engineering of the original backbone are available. For example, modification of somatostatin (An eight amino acid-long peptide) resulted in half-life prolongation from a few minutes to more than one day without generating side effects.

The blockbuster medicine octreotide was developed as a result of work in the field of chemistry (Lamberts and Hofland, 2019). Analogues of endogenous peptides have also been coupled with an albumin binding motif to further enhance their pharmacological profile. This method enabled the creation of incretin (liraglutide) and long-acting insulin (detemir) medications (Ahmadi *et al*., 2022). According to Bech *et al.* (2018), molecules with an albumin binding motif bind albumin non-covalently, resulting in a lengthy half-life and decreased renal excretion.

Research on the management of reproduction is mainly focused on females. This has proven to be an effective approach leading to most of the available methods for both ovulation induction (Caraty *et al*., 2007; Pottapenjera *et al*., 2018; Leonardi *et al*., 2020) and contraception (Clarke and Dhillo, 2016). The first aspect is more relevant to livestock management, and despite the success of current methods, there is significant scope for improvement. The main limits of current methods reside in environmental liability, health risk and reduced efficacy over time. For example, the use of pregnant mare serum gonadotropin (PMSG) comes with sanitary risks because the molecule is extracted from biological fluids and has reduced efficacy over time due to the development of an immune reaction against the molecule itself. Substituting PMSG with a drug deprived of this liability would be a significant advantage. Hence, the discovery of the Kp system filled this gap, and new strategies to tune reproduction by finely modulating GnRH release is now possible. Various Kp agonists are compound 17, C6, hKp10, oKp10, eKp10, FTM080, FTM145, TAK-488, TAK-683 (Beltramo and Decourt, 2018).

Conclusion

The kisspeptin neural system, which controls both the pulsatile and surge forms of GnRH release, is crucial in its function as the gatekeeper of reproduction, according to recent findings. Even though translational and field investigations by a few groups have only begun, the biological actions of kisspeptin strongly indicate that analogs of kisspeptin and NKB would be useful in the development of new strategies for the regulation of fertility in domestic animals.

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