Review Article

Kisspeptin signalling in the control of the gonadotropic axis

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Abstract

Ever since the discovery of the role of kisspeptin-GPR54 signalling in puberty, kisspeptin has been the focus of intense research to elucidate the implication of this neurohormone in the control of the gonadotropic axis. Kisspeptin is now a well-established stimulator of the gonadotropin-releasing hormone (GnRH) secretion. Kisspeptin neurons in the arcuate nucleus mediate negative feedback on gonadotropic activity and appear to be at the core of the GnRH / luteinizing hormone (LH) pulse generator. Kisspeptin neurons of the anteroventral periventricular area are essential for both the generation and the timing of the preovulatory LH surge. These neurons also mediate the positive feedback of sex steroids necessary for the LH surge. As kisspeptin can act directly on GnRH terminals in the median eminence located outside of the blood brain barrier, kisspeptin signalling is a prime target for therapeutic developments targeting the control of fertility for contraception or medically assisted procreation, as well as the treatment of reproductive disorders.

Key words: Kisspeptin, Arcuate nucleus, Anteroventral periventricular area, Gonadotropic axis, Gonadotropin-releasing hormone, Luteinizing hormone

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Introduction

The function of the reproductive system is to ensure survival of the species. The reproductive system is responsible not only for the production of egg and sperm cells, but also for sustaining these cells and the development of the offspring. Some disorders in the reproductive function result in the failure to conceive, leading to infertility.

Contraception either prevents fertilization of the egg by the sperm by physical barriers or hormonal methods. Current strategies for contraception mainly target egg production and fertilization using sex steroid analogues. These treatments are associated with non-negligible side effects. Understanding the normal reproductive anatomy and physiology is essential to manipulate the reproductive function both for contraception and the treatment of infertility. In the brain, a group of neuroendocrine cells within the hypothalamo-pituitary-gonadal (HPG) axis plays a key role in controlling reproduction and pubertal maturation through the stimulation of gonadotropin releasing hormone (GnRH) secretion.[1] Controlling the HPG axis at the level of GnRH neurons or their downstream effectors has been suggested as a key to develop treatments of reproductive disorders.

Kisspeptins, the products of the Kiss1 gene were originally identified in 1996 as 'metastin' because of their capacity to suppress tumour metastasis in breast cancer and melanoma.[2 - 4] However, a new critical role of kisspeptins and its receptors (GPR54 / Kiss1R) in reproduction was discovered in 2003. Absence of GPR54 induces the hypogonadotropic hypogonadism (HH) and consequent infertility in humans and mice.[5 - 7] In addition, studies in several mammalian species have been identified kisspeptin cells as major regulators of GnRH neurons. A selective kisspeptin antagonist suppresses gonadotropin pulse frequency in a dose-dependent manner.[8 - 10] Recent studies in ewes demonstrated an essential role of kisspeptin in the stimulation of GnRH release and the preovulatory LH surge.[11] Furthermore, recent reports in human have been shown that kisspeptin stimulates gonadotropin secretion in women, and the kisspeptin secretion is modulated by the sex steroid feedback.[12] These findings illustrate the key role of the kisspeptin system as a critical regulator of reproduction, suggesting a new therapeutic target for the control of human reproduction.

KISS1/GPR54 system

In the periphery, kisspeptin was first discovered in the placenta, and has since been described in a variety of other structures such as the gonads, pancreas and intestine.[13, 14]

In the central nervous system (CNS), kisspeptin neurons are located in two structures, the anteroventral periventricular area (AVPV) and the arcuate nucleus (ARC). Kisspeptin acts through the G protein-coupled receptor GPR54 on GnRH neurons in the hypothalamus, and is considered the most potent stimulator of GnRH release in mammals, including human, monkey, sheep, rat and mice.[15 - 17]

Kisspeptin structure

Kisspeptins are encoded by the *KISS1/Kiss1* gene and are derived by differential proteolytic processing from a single precursor protein (145 amino acid peptides), producing shorter fragments of the carboxyl (C)-terminal region of the molecule with 54 (Kp-54), 14 (Kp-14), 13 (Kp-13) and 10 (Kp-10) amino acids. Kisspeptin 54 (Kp-54), the largest and most abundant proteolytic product was previously known as 'metastin'. Kisspeptins are members of RFamide peptide superfamily because they all share arginine-phenylalanine residues at the carboxy terminus, which is also amidated (thus RFamide). This amidated RF carboxy terminus in all kisspeptin forms is critical for their biological activity.[18] Kisspeptin 10 (Kp-10) represents the smallest form of kisspeptin that is able to fully activate the kisspeptin receptor.

G protein-coupled receptor 54 (GPR54)

GPR54 was first described in the rat brain in 1999 as an orphan receptor. This seven transmembrane domain G protein-coupled receptor comprises 369 amino acids[19] binds 'metastin', the original name of Kp-54, a product of KISS1 gene.[13, 20, 21] All the smaller proteolytic fragments of the Kiss1 precursor, Kp-14, Kp-13 and Kp-10, also bind to GPR54 and activate the receptor. The structure of GPR54 shows a sequence similarity (> 40%) to the GAL1 galanin receptors. However, galanin does not bind to GPR54.[19]

Kisspeptin-GPR54 signalling pathway

GPR54 is a GPCR, coupled to $G_{q/11}\alpha$. Kisspeptin binding to this receptor activates phospholipase C (PLC), triggering the hydrolysis of phosphatidylinositol bisphosphate (PIP2) into inositol 1,4,5-trisphospate (IP3) and diacylglycerol (DAG). IP3 then releases Ca^{2+} from the endoplasmic reticulum. The increased intracellular Ca^{2+} concentration together with the DAG lead to the activation of protein kinase C (PKC) and the phosphorylation of mitogen-activated protein kinases (MAPKs), such as ERK1/2 and p38. Furthermore, GPR54 signalling is modulated by the recruitment of beta-arrestin. Recruitment of beta-arrestin1 results in decreased GPR54-mediated ERK phosphorylation. In an opposite manner, recruitment of beta-arrestin2 results in increased GPR54-mediated ERK phosphorylation.[22]

Distribution of KISS1/kisspeptin in the central nervous system

A number of anatomical studies using both in situ hybridization (ISH) and immunocytochemistry (ICC) in various mammalian species, including humans, have analysed the distribution of Kiss1 neurons and their fibres in the nervous system.[23] As previously stated, kisspeptin neurons are found mainly in two locations. The most important population is located in the arcuate nucleus (ARC) or its primate equivalent the infundibular nucleus. A second population is found in the medial preoptic area (MPOA) and more specifically in the anteroventral periventricular area (AVPV). This second population displays a sexual dimorphism in most species, with a higher number of kisspeptin neurons in females compared to males.

Minor populations of kisspeptin neurons have also been described in the medial amygdala and the bed nucleus of the stria terminalis (BNST)[24]. Initial reports of kisspeptin neurons in the DMH and VMH by ICC have not been confirmed by ISH or transgenic approaches and are most likely due to cross-reaction of kisspeptin antibodies with the related RFamides RFRP-1 and RFRP-3.

Kisspeptin fibres have been identified in the areas of kisspeptin neuron cell bodies, as well as a variety of hypothalamic and extrahypothalamic structures, most notably around GnRH neurons in the forebrain and in the internal zone of the median eminence.[23 - 25] Caution has to be applied to these reports as several commonly used kisspeptin antisera have since been shown to cross-react considerably with another RFamide, namely RFRP also known as gonadotropin inhibitory hormone (GnIH). While dilution of antisera can reduce this cross-reaction in cell bodies, the high local concentration of neuropeptides in axons does not allow confirmation of specific labelling by this approach. Nevertheless, the presence of direct synaptic contacts of kisspeptin fibres onto GnRH neurons is well established today. Also, the presence of kisspeptin terminals in the vicinity or in direct contact with GnRH terminals in the median eminence has been verified by several studies.

More recently, Yip and co-workers used conditional viral tract tracing on Kiss-Cre mice to identify the projections of the two major kisspeptin neuron populations located in the AVPV and the ARC. Only AVPV neurons seem to project directly onto GnRH neuron cell bodies, while the ARC kisspeptin neurons project mainly onto the GnRH terminals in the median eminence. Interestingly, the ARC kisspeptin neurons also appear to project to the AVPV kisspeptin neurons, but not to the GnRH neurons themselves. The AVPV neurons also project to the median eminence, but as this population is smaller than the ARC kisspeptin neuron population (particularly in males), this AVPV – median eminence projection is smaller than the ARC – median eminence projection.[26]

Kisspeptin controls reproductive function via the HPG axis

The hypothalamo-pituitary-gonadal (HPG) axis is the regulator of normal reproductive function and pubertal maturation. The function of this neurohormonal system relies on the connection and feedback between three major groups of cells in; 1) the hypothalamus, synthesis and release of GnRH, 2) the pituitary gland, synthesis and release of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and 3) the gonads, synthesis and release of sex steroids (testosterone, estrogen and progesterone) in addition to the production of gamete. Malfunction of the HPG axis can cause the deficiency of gonadotropin secretion, which leads to

abnormal sexual differentiation during fetal life, abnormal pubertal maturation and infertility.

Genetic studies have demonstrated that the kisspeptin/GPR54 system is involved in the control of gonadotropin secretion. Lack of functional GPR54, leads to hypogonadotropic hypogonadism (HH), which is characterized by hypogonadism due to a deficiency of gonadotropin secretion from the pituitary gland, resulting in a failure of puberty both in humans and mice.[5, 7] Conversely, in 2008, Teles and co-workers identified a patient with a KISS1R-activating mutation that trigger precocious puberty.[27] These findings triggered the discovery of a new role of kisspeptins in reproductive functions in addition to its role in tumour metastasis suppression.[2 - 4] Moreover, both anatomical and physiological studies in mammalian species have demonstrated that kisspeptin cells, scattered in hypothalamus interact directly with GnRH cells, stimulating gonadotropin release.[10, 16, 28]

Connections between kisspeptin and GnRH neurons

Anatomical studies have shown that kisspeptin cells are located mainly in the ARC and AVPV, while their fibres are projected mainly to the ARC itself and the internal zone of median eminence. Moreover, kisspeptin fibres were also found in the preoptic region with some of them making direct contacts with GnRH neurons.[17] GPR54/Kiss1R expression in GnRH neurons has first been shown using LacZ reporter expression under the control of the GPR54 promoter in Gpr54-/- knockout mice, using the LacZ insertion into the Gpr54 locus.[8] In 2010, Herbison and co-workers confirmed these results in hemizygous Gpr54 mutant mice.[29] GPR54 is also expressed in a variety of immortalized GnRH expressing neuronal cell lines.[30 - 32] More recently, Higo and co-workers have been able to demonstrate the presence of both GnRH and GPR54 transcripts in the same neurons in normal rats.[33] A direct action of kisspeptin on GnRH neurons was already suggested in 2004 by Irwig and co-workers[16], who showed that the kisspeptin induced gonadotropin release can be blocked by acycline, a GnRH antagonist. Moreover, a selective kisspeptin antagonist was shown to inhibit the firing of GnRH neurons in the mouse brain and to reduce pulsatile GnRH secretion in monkey.[28] Administration of a kisspeptin receptor agonist results in increased LH plasma concentration in ewes.[34] These anatomical, molecular and physiological findings support a direct action of kisspeptins on GnRH neurons for the control of reproductive activity.

Regulation of kisspeptin neurons by sex steroid hormones

One of the key features of the gonadotropic axis is the feedback control through the sex steroids, mainly testosterone and estrogen. This feedback control acts both directly on pituitary gonadotropes and on the brain. However, the exact site of sex steroid feedback control in the brain has remained elusive until the discovery of kisspeptin neurons.

In male rodents, Kiss1 expression in the ARC appears to be regulated by testosterone. Castrated male rats[16] and mice[35] show a marked up-regulation of Kiss1 expression in the ARC, which is prevented by testosterone replacement in post-castrated animals. The AVPV kisspeptin neurons responded in a reverse manner to castration, with a marked reduction following castration and a restoration of kisspeptin expression after testosterone replacement.[35] These findings suggested that kisspeptin cells in the ARC are involved in the negative feedback control of GnRH/LH secretion. Conversely, kisspeptin cells in AVPV are suggested to relay positive feedback control of GnRH/LH secretion.[35]

In female rodents, circulating levels of gonadal hormones determine the expression of Kiss1 and its protein in a site-specific manner as well as in male. Upregulation of Kiss1 expression in the ARC was induced in ovariectomized mice and was reduced by estrogen replacement.[35] In the AVPV again, ovariectomy abolished kisspeptin expression, which could be restored by estradiol replacement.[36] Thus similar to males, kisspeptin cells in the female ARC seem to relay negative feedback control of GnRH/LH secretion, while the AVPV kisspeptin neurons relay a positive feedback control of GnRH/LH secretion.[36]

Studies using knockout mice had already shown that estrogen receptor alpha was essential for both the positive and negative feedbacks of sex steroids.[37 - 39] Only a small subset of GnRH neurons expresses estrogen receptor beta and never estrogen receptor alpha. Thus GnRH neurons cannot be the site of sex steroid feedback onto the HPG axis. Kisspeptin neurons both in the AVPV and the ARC express estrogen receptor alpha[40 - 42] and kisspeptin expression is directly regulated by estrogen receptor alpha.[43] Finally, immunotoxin ablation of ARC kisspeptin neurons abolishes the rise in circulating LH after ovariectomy in female rats, although it does not completely abolish negative feedback of estrogen.[44] These observations establish ARC kisspeptin neurons as a key relay in the negative feedback of sex steroids.

Kisspeptin and the GnRH pulse generator

In 2007, Goodman and co-workers reported that most ARC kisspeptin neurons also co-express the tachykinin peptide neurokinin B (NKB) as well as the endogenous opioid peptide dynorphin A (Dyn).[45] Neurokinin B was previously known to be a regulator of the gonadotropic axis. In 2009, Guran et al.[46] and Topaloglu et al.[47] reported that mutations in the TAC3 gene (encoding neurokinin B) and the TACR3 (encoding the neurokinin receptor 3) resulted in hypogonadotropic hypogonadism as mutations for kisspeptin and/or its receptor. These discoveries clearly implicated interactions between neurokinin B and kisspeptin in the control of the gonadotropic axis. The ARC kisspeptin neurons have since been designated as KNDy ("Kennedy") neurons due to their co-expression of the 3 neuropeptides kisspeptin, NKB and Dyn.

Neurokinin B is an activator of the gonadotropic axis similar to kisspeptin. In vivo electrophysiological studies of KNDy neurons showed that this population of neurons displayed synchronized bursts of electrical activity, each of which was followed by an LH pulse.[48] Thus these synchronized bursts are the electrophysiological manifestation of the GnRH/LH pulse generator. Administration of NKB increased the frequency of these electrical activity burst, while administration of Dyn reduced this frequency. Furthermore, ARC kisspeptin neurons are surrounded by nerve terminals containing kisspeptin, NKB and Dyn, suggesting that ARC kisspeptin neurons are interconnected by a network of axon collaterals derived from these very same neurons. Finally, ARC kisspeptin neurons express both the NK3R NKB receptor and the kappa opioid receptor.[49]

Combining these observation, Wakabayashi and co-workers[48] proposed that the KNDy neuron population is a pulse generator based on a neuronal network alternatively stimulated by NKB and inhibited by Dyn. ARC KNDy neurons express hyperpolarization-activated cyclic nucleotide-regulated and calcium channels required for generating pacemaker potentials.[50] A KNDy neuron triggering pacemaker potential will activate the surrounding KNDy neurons through NKB-NK3R signalling, generating an excitation wave propagating itself through KNDy neuron population and the synchronized burst of electrical activity necessary for a GnRH / LH pulse. The co-secreted dynorphin is supposed to act slower to eventually shut down the electrical activity and the cycle can start again to generate the next pulse. Thus the ARC KNDy neurons appear to be a key actor in both the negative feedback of sex steroids on the gonadotropic axis, as well as in the generation of the GnRH / LH pulses.

The AVPV kisspeptin neurons and the preovulatory LH surge

A key feature of the preovulatory LH surge is the fact that during this surge estrogen feeds back positively on the gonadotropic axis. AVPV kisspeptin neurons present a positive feedback of sex steroids on kisspeptin expression. Furthermore, the sexual dimorphism with a higher number of AVPV kisspeptin neurons in females than in males already suggested a particular role of this population in females.

Kisspeptin neurons in the AVPV present a high level of immunoreactivity for the immediate early gene c-Fos (a neuronal activation marker) coincident with the LH surge.[40, 42] Furthermore, kisspeptin expression is regulated by the oestrus cycle, displaying an increase of kisspeptin mRNA levels only on the evening of proestrous, and not during diestrous.[40, 42, 51] Also, a notable reduction in kisspeptin immunoreactivity in AVPV neurons is observed

on the evening of proestrous, coincident with the LH surge and the peak of kisspeptin mRNA levels, suggesting a massive release of kisspeptin at the moment of the LH surge.[51] Finally, immunoneutralization of released kisspeptin using an infusion of anti-kisspeptin antibodies into the AVPV at the moment of the LH surge is able to block the LH surge.[42] These observations have clearly established the key role of AVPV kisspeptin neurons in the production of the preovulatory LH surge.

A key feature of this preovulatory surge is its precise circadian timing. The AVPV region receives a direct vasopressinergic input from the suprachiasmatic nucleus (SCN), the mammalian central circadian clock.[52] Vasopressin is one of the main circadian outputs of the SCN circadian clock, and central administration of vasopressin is able to trigger an LH surge in ovariectomized female rodents with estradiol supplementation.[53] Thus the circadian timing of the LH surge on the day of proestrous might be generated through the interaction of the positive feedback of estradiol through estrogen receptor alpha on AVPV kisspeptin neurons coinciding with a circadian vasopressin signal originating in the SCN. However, the involvement of a local peripheral circadian oscillator in the AVPV kisspeptin neurons is currently under investigation.[51]

Kisspeptin in puberty and seasonal reproduction

Kisspeptin's role in reproduction has been discovered initially through its role in puberty, both in rodents and in humans. Interference with kisspeptin signalling, either through invalidation of the kisspeptin gene itself or its receptor GPR54/Kiss1R, results in hypogonadotrophic hypogonadism, clearly illustrating the critical role of kisspeptin signalling in puberty.[5 - 7] In rats, kisspeptin mRNA expression can only be detected after postnatal day 15, but shows a significant increase around puberty.[54] Similarly, kisspeptin immunoreactivity shows a maturation of the kisspeptin system only around the time of puberty.[55] And finally, precocious puberty can be triggered in rodents through central administration of kisspeptin during the prepubertal period[56] and through GPR54 activating mutations in humans.[27]

These observations have now firmly established the role of kisspeptin in puberty and the adult regulation of the gonadotropic axis. These facts also triggered a strong interest for the potential involvement of kisspeptin in the seasonal regulation of reproduction. Many mammal species reproduce only during certain seasons of the year. Their offspring is born and weaned in spring and summer where food is readily available for both the offspring and the mother. To do so, they have to activate their gonadotropic axis during a season that has to take into account the gestational period. Animals with a short gestational time of one month (most rodents) or a gestational time close to one year are sexually active during spring. On the other hand, if gestational time is around six months (e.g. sheep), the sexual activity will occur in fall. Outside of these periods, the gonadotropic axis is inactive, resulting in low circulating LH levels and atrophied gonads and reproductive organs. The synchronization of the reproductive activity is controlled by the length of the day light period and its influence on nocturnal pineal melatonin secretion. In summer, long days result in short nightly melatonin peaks, while the long winter nights result in long melatonin peaks. The duration of the nightly melatonin peak has long been recognized as the key factor controlling seasonal reproduction.

In 2006, Revel and co-workers showed that kisspeptin levels were low in sexually inactive Syrian hamsters. Furthermore, they showed that the length of the melatonin peak controls kisspeptin expression in the ARC. And finally, intracerebroventricular infusions of kisspeptin were able to completely reactivate the seasonally inhibited gonadotropic axis.[57] The implication of kisspeptin in seasonal breeding has since been confirmed in other species such as sheep.[58] More recently, Klosen and co-workers have shown that intracerebroventricular infusion of thyroid stimulating hormone (TSH), a signal controlled by melatonin but locate upstream of kisspeptin, is also able to fully restore the gonadotropic activity and in doing so reactivates also kisspeptin expression.[59] Thus kisspeptin is now also established as a key actor in seasonal control of the gonadotropic axis.

Role of kisspeptin in humans

Kisspeptin was initially named metastin because it had been identified as a metastasis suppressor in melanoma cells. The receptor for metastin was then shown to be GPR54, now called Kiss1R. In 2004, the role of GPR54 signalling in the control of reproduction was discovered, but metastin expression had already previously been shown in the placenta. Maternal plasma concentrations of metastin increase throughout gestation and return to non-pregnant levels after delivery, suggesting that circulating metastin during pregnancy is mainly derived from the placenta.[60]

Kisspeptin-54 was first tested to stimulate the HPG axis in human males in 2005. The results demonstrated that intravenous infusion of kisspeptin-54 could increase circulating LH, FSH and testosterone levels in male volunteers.[61] Moreover, subcutaneous bolus injection of kisspeptin-54 in female volunteers could increase plasma LH level in preovulatory phase compared with saline injection in all phases of menstrual cycle.[62] In addition, kisspeptin-10 administration in both healthy men and women could stimulate gonadotropin release in men as well as women. However, serum LH and FSH were elevated only during the preovulatory phase of the menstrual cycle but failed to be elevated during follicular phase.[63] These findings provide a novel mechanism for HPG axis manipulation in human reproductive disorders.

A number of kisspeptin studies in women show therapeutic effects of kisspeptin on LH release. In women with infertility due to hypothalamic amenorrhea, high doses of kisspeptin-54 acutely increased LH secretion, but chronic administration resulted in desensitization of the system.[64] Although chronic kisspeptin administration causes the tachyphylaxis in women with hypothalamic amenorrhea, chronic exposure to kisspeptin-54 in healthy women does not abolish a normal menstrual cycle.[65] Furthermore, administration of kisspeptin-54 temporarily increases LH pulsatility in both healthy women and women with hypothalamic amenorrhea.[65, 66]

During pregnancy, kisspeptin level are not only elevated in the blood[60], but elevated kisspeptin levels can also be detected in the urine.[67] Thus, urinary kisspeptin levels may provide a clinically useful and non-invasive means of evaluating circulating kisspeptin levels during pregnancy. Circulating kisspeptin levels could be used as a marker of reproductive development in children and to diagnose the risk of miscarriage in pregnant women.[68] Indeed, low circulating kisspeptin-10 levels are observed in women with early pregnancy bleeding.[69] Also, significantly lower plasma kisspeptin levels can be observed in women who went on to suffer miscarriage.[68] In addition, kisspeptin-54 can safely trigger oocyte maturation in women at high risk of ovarian hyperstimulation syndrome during IVF therapy.[70] Kisspeptin-54 administration in healthy and non-healthy women triggered no changes in other pituitary hormones both after acute and chronic administration. This underlines the therapeutic potential of kisspeptin to treat patients with reproductive disorders.

Conclusion

Kisspeptins, the products of the Kiss1 gene, and their receptor, GPR54 / Kiss1R were discovered as key regulators of the HPG axis upstream of GnRH / LH secretion. Kisspeptin neurons located in the arcuate nucleus appear essential for negative feedback of sex steroids on the gonadotropic axis and might be the long sought after GnRH / LH pulse generator. Kisspeptin neurons in the forebrain (AVPV) are key actors for both the generation and the timing of the preovulatory LH surge. Reproduction also requires adequate metabolic reserves. Kisspeptin neurons appear to integrate metabolic cues to determine whether an organism is fit to engage in reproduction.[71, 72] Thus kisspeptin neurons appear as the “gatekeepers” of reproduction (Figure 1).

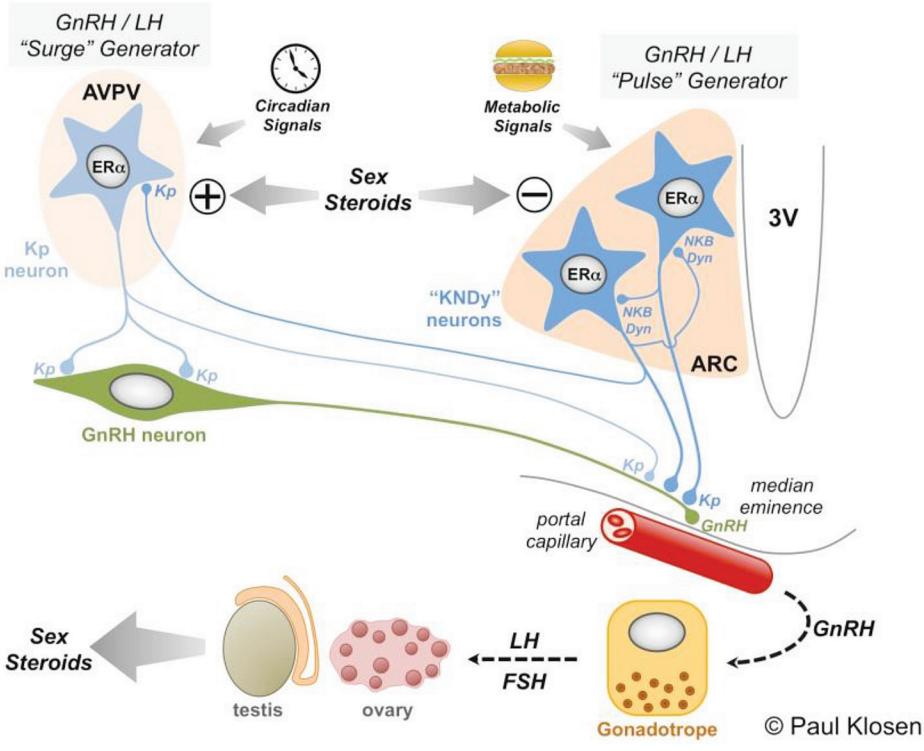

Figure 1 Kisspeptin and the gonadotropic axis

Kisspeptin neurons are located mainly in two structures, the anteroventral periventricular nucleus (AVPV) and the arcuate nucleus (ARC, infundibular nucleus in primates). Both populations project to the gonadotropin releasing hormone (GnRH) neurons. The AVPV neurons contact mainly to the cell body, but some connections with the GnRH terminals in the median eminence exist. The ARC neurons contact mainly the GnRH terminals in the median eminence and send some collaterals to the AVPV kisspeptin neurons. Reciprocal connections exist between the ARC kisspeptin neurons, called Kennedy neurons (KNDy) because they co-express Kisspeptin (Kp), Neurokinin B (NKB) and Dynorphin A (Dyn). This network of kisspeptin neurons controls GnRH secretion and thus the gonadotropic axis comprised of the hypothalamic GnRH neurons, the pituitary gonadotropes and the gonads. Sex steroids feed back positively on the AVPV kisspeptin neurons and negatively on the ARC KNDy neurons. The AVPV neurons are responsible for the preovulatory GnRH / LH surge through the coincidence of the positive feedback of estrogen and a circadian signal probably provided by the circadian clock of the suprachiasmatic nucleus. ARC KNDy neurons are probably the core of the GnRH / LH pulse generator and also integrate metabolic signals to determine whether the organism is fit to engage in reproduction. (3V – third ventricle, LH – luteinizing hormone, FSH – follicle stimulating hormone)

Importantly, kisspeptin is able to act directly on GnRH terminals in the median eminence located outside of the blood brain barrier, opening the possibility to use peripheral administration of kisspeptins for therapeutic use. In humans, peripheral administration of kisspeptin stimulates gonadotropin release in healthy women as well as in men and restores the GnRH/LH pulsatility in women with hypothalamic amenorrhea. These data suggest the potential of kisspeptin to treat patients with infertility. Moreover, kisspeptin plasma and urinary levels could be used as markers of reproductive development in children and to evaluate the risk of miscarriage in pregnant women.

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บทคัดย่อ

การส่งสัญญาณของคิสเปปตินในการควบคุมแกนควบคุมระบบสืบพันธุ์

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สาขากายวิภาคศาสตร์ สถานวิทยาศาสตร์พรีคลินิก คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

นับตั้งแต่มีการค้นพบบทบาทการส่งสัญญาณของคิสเปปติน-จีพีอาร์๕๔ ต่อวัยเจริญพันธุ์ ฮอร์โมนประสาทนี้ได้ถูกนำมาศึกษาในงานวิจัยเพื่อมุ่งอธิบายถึงบทบาทในการควบคุมแกนควบคุมระบบสืบพันธุ์ ปัจจุบัน คิสเปปตินจัดเป็นตัวกระตุ้นที่ทำให้เกิดการหลั่งโกนาโดโทรปินรีลิสซิ่งฮอร์โมน เซลล์ประสาทคิสเปปติน บริเวณอาร์คิวเอทนิวเคลียส ทำหน้าที่เป็นสื่อกลางทำให้เกิดการยับยั้งย้อนกลับต่อฤทธิ์ของโกนาโดโทรปินและเป็นตัวการหลักในการให้กำเนิดสัญญาณของโกนาโดโทรปินรีลิสซิ่งฮอร์โมน/ลูทิไนซิ่งฮอร์โมน ส่วนเซลล์ประสาทคิสเปปตินบริเวณแอนทีโรเวนทรอลเพอริเวนตริคูลาร์ มีบทบาทสำคัญในการให้กำเนิด และกำหนดเวลาในการเพิ่มขึ้นของระดับลูทิไนซิ่งฮอร์โมนก่อนการตกไข่ รวมถึงเป็นสื่อกลางที่ทำให้เกิดการกระตุ้นย้อนกลับต่อฤทธิ์ของฮอร์โมนเพศส่งผลให้เกิดการเพิ่มขึ้นของลูทิไนซิ่งฮอร์โมน นอกจากนี้พบว่า คิสเปปตินสามารถส่งสัญญาณไปที่ปลายประสาทของโกนาโดโทรปินรีลิสซิ่งฮอร์โมนในมีเดียนเอมีเนนส์ได้โดยตรง จากข้อมูลเหล่านี้แสดงให้เห็นว่าสัญญาณจากคิสเปปตินมีความสำคัญในการนำไปใช้พัฒนา การรักษาทางการแพทย์ เพื่อควบคุมภาวะเจริญพันธุ์หรือใช้เป็นตัวช่วยเพื่อให้กำเนิดบุตร เช่นเดียวกับการนำไปใช้ในการรักษาความผิดปรกติทางระบบสืบพันธุ์

คำสำคัญ: คิสเปปติน, อาร์คิวเอทนิวเคลียส, บริเวณแอนทีโรเวนทรอลเพอริเวนตริคูลาร์, แกนควบคุมระบบสืบพันธุ์, โกนาโดโทรปินรีลิสซิ่งฮอร์โมน, ลูทิไนซิ่งฮอร์โมน