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REVIEW ARTICLE

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Kisspeptin Hormone: Revolution in Reproductive System Physiology

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Abstract

The control of reproduction has been attributed to the actions and feedforward of the sex steroids gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). However, recent findings, including the identification of kisspeptin neurons and a kisspeptin-GnRH-LH/FSH axis, have prompted a reevaluation of reproductive regulation. At first, the *KISS1* gene encoding kisspeptin was thought to belong to a group of genes called metastasis suppressors. Vertebrate and mammalian genomes have been enriched with *Kiss* and *KissR* gene variations during the last two decades. In 2003, kisspeptins and their receptor, *KISS1R*, and their role in the neuroendocrine-reproductive axis were discovered. This finding radically altered our understanding of reproductive physiology. These discoveries support the role of kisspeptins and their receptor as gatekeepers of sexual maturity at the outset of puberty and as key processors in the adult-life dynamic control of the gonadotropic axis. The significance of kisspeptin signaling in spermatogenesis and sperm quality is still debatable, even though *Kiss1* and *Kiss1R* are expressed peripherally in the testes. Numerous processes, including steroidogenesis, follicular maturation, ovulation, and ovarian senescence, are affected by kisspeptin activity. Therefore, kisspeptin analogs (both agonists and antagonists) may be useful as therapies for those with disorders affecting the reproductive system. This overview focuses on the evolution, localization, and reproductive importance of the Kiss–KissR pair. **(International Journal of Biomedicine. 2023;13(4):197-206.)**

Keywords: kisspeptin • KISS1• KISS1R• kisspeptin analogs • kisspeptin-GnRH-LH/FSH axis

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Abbreviations

GnRH, gonadotropin-releasing hormone; **LH**, luteinizing hormone; **FSH**, follicle-stimulating hormone; **HPG** axis, hypothalamus-pituitary-gonadal axis; **HH**, hypogonadotropic hypogonadism; **KsRE**, kisspeptin-response element; **KNDy**, kisspeptin/neurokinin B/dynorphin; **SPZ**, spermatozoa; **IVF**, in vitro fertilization; **OHSS**, ovarian hyperstimulation syndrome.

Introduction

The *KiSS-1* gene (HGMW-approved symbol, *KISS1*) encoding for a hydrophobic 145 amino acid protein called kisspeptin was discovered in 1996 by Lee et al.[1] as a malignant melanoma metastasis-suppressor gene. It was named "*KISS1*" so that everyone would know where it was discovered, namely in Hershey, Pennsylvania, home of the famous Hershey Kisses chocolates. The "SS" in KISS1 stands for "suppressor sequence" to honor its role in gene regulation. In humans, the *KISS1* gene is located on the long (q) arm of chromosome 1 at q32 with four exons.[1,2] Post-translational processing of the 145-amino-acid intermediate prepropeptide encoded by *KISS1* yields four physiologically active peptides with distinct molecular weights: kisspeptin-54, kisspeptin-13, kisspeptin-10, and kisspeptin-14 (Figure 1).[3] All these peptides have a C-terminal region that contains an Arg–Phe–NH2 motif characteristic of the RF-amide peptide family, which allows them to bind to and fully activate the kisspeptin receptor (KISS1R).[4-6] In many mammals, kisspeptins stimulate the release of GnRH (and subsequently the secretion of FSH and LH) by binding to the KISS1R, which belongs to the G-protein-coupled receptor family.[7]

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This seven-transmembrane receptor is structurally similar to the transmembrane region of galanin receptors, with ~40% sequence identity.[4]

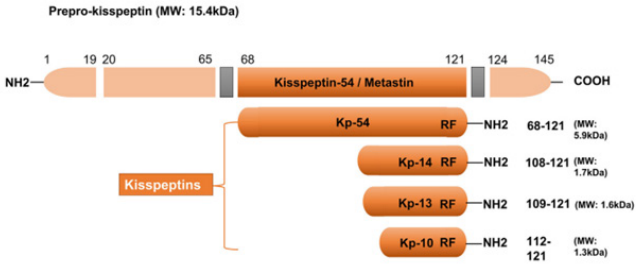

Fig. 1. *Human kisspeptins, products of the KISS1 gene. "Different kisspeptins are generated by the cleavage from a common precursor, the prepro-kisspeptin. The prepro-kisspeptin contains 145 amino acids, with a 19-amino acid signal peptide and a central 54-amino acid region, kisspeptin-54 (Kp-54; formerly termed as metastin). Further cleavage of metastin generates kisspeptins of lower molecular weight: kisspeptin-14 (Kp-14), Kp-13, and Kp-10. All kisspeptins contain the RF-amide motif that is able to bind and activate kisspeptin receptor."*[3]

Kisspeptins were utilized universally to describe this class because of their structural similarity and shared ancestry as KISS1-derived peptides.[8,9] Kisspeptin-54 was initially termed "metastin" because of its capacity to inhibit tumor metastasis. This peptide has been considered as the major product of the human KISS1 gene.[10] The larger peptide comprises some variability among species, whereas the 10 amino acid C-terminus peptide is well conserved and binds to and activates KISS1R.[1,5,6,11]

A later cloning effort resulted in identifying the human homolog of KISS1 as a putative receptor for KISS1-derived peptides in several databases. Multiple laboratories have independently identified and/or investigated the physiological functions of KISS1R (also known as GPR54, AXOR12, hOT7T175, CPPB1, and HH83).[12] A revolution in reproductive physiology began with the 2003 discovery of kisspeptins and their receptor in the neuroendocrine-reproductive axis.[13,14] These findings support the role of kisspeptins and their receptor as gatekeepers of sexual maturity at the outset of puberty and as key processors in the adult-life dynamic control of the gonadotropic axis.

De Roux et al.[15] reported on a family affected by HH in 2003. These individuals shared a deletion of 155 nucleotides in the orphan receptor gene *GPR54* [or *KISS1R*], encoding a G protein-coupled receptor, which impeded the onset of puberty and the development of reproductive organs. Using genetic engineering, Seminara et al.[16] induced the same defect in the *Gpr54* gene of mice, discovering disruptions in puberty and reproductive processes. This demonstrated the critical role of *GPR54* in reproductive regulation. Kisspeptin-54 and kisspeptin-10 were found to be *GPR54* ligands.[2,17,18] It was subsequently shown that hypothalamic neurons carrying kisspeptin send axons to GnRH neurons that express KISS1R.[19-22] In addition, estrogen receptor alpha (ERα) expression was detected in kisspeptin neurons.[23] These results showed that kisspeptin neurons are downstream of GnRH neurons and receive direct peripheral feedback of sex steroid hormones via KISS1R. Multiple neuropeptides, such as GABA and glutamate (which is also input to GnRH), have been proposed to be involved with kisspeptin neurons; however, these are better understood as neurons involved with adjusting the function of the large performing kisspeptin neural cells than as neurons downstream of kisspeptin neurons. Because of this, kisspeptin is an integral part of the feedback system that regulates the GnRH-LH/FSH axis.

In the last 25 years, researchers have made significant progress in understanding the signaling processes of biological systems thanks largely to kisspeptins and their receptor, Kiss1R.[24] In 2003, it was discovered that HH, characterized by deficiencies in GnRH secretion, gonadotropin discharge, and infertility, is caused by inactivating mutations in the human *KISS1R* gene.[14,25] Its biological role has broadened from cancer progression to reproduction, fertility, and energy homeostasis since the system was first characterized in non-mammalian vertebrates,[26,27] and Kiss1 and Kiss1R were found to be expressed (at the mRNA and protein levels) in peripheral tissues such as gonads, placenta, pancreas, adipose tissues, liver, and vasa.

Kiss1 and Kiss1R in Regulating Fertility

The generation of gametes is regulated by endocrine, paracrine, and autocrine communications between the pituitary (which secretes gonadotropins like FSH and LH, among others) and the gonads (which secrete sex steroids like testosterone). Humans and animal models with mutations in the *KISS1/KISS1R* genes exhibit precocious puberty and HH due to stimulation or dysfunction of the hypothalamic HPG axis.[14,25,28-30] Specifically, the neurohormone GnRH is produced and secreted by neuronal populations regulated by kisspeptin in the arcuate nucleus and the anteroventral periventricular nucleus.[31]

Kisspeptin's influence on *GnRH* gene expression is mediated by dynamic chromatin changes that it creates.[32,33] Kisspeptin-response element (KsRE) in the mouse genome, located at positions -3446 and -2806, and on GnRH-neuronal cell lines, and mutant mice were used to locate an enhancer of the *GnRH* gene. Orthodenticle Homeobox 2 (Otx-2) is a transcription factor whose binding site is encoded by the *KsRE* gene. To activate *GnRH* gene transcription, kisspeptin treatment first creates nucleosome-depleted DNA in KsRE, which then promotes Otx-2 gene transcription and protein synthesis.[32] Kisspeptin influences recognized indicators of active chromatin, but it has no impact on repressive markers of genes; the fact that it enhanced acetylation of histone 3 (H3) at lysine (K)14 and (K)27 and trimethylation of H3K4 inside the KsRE is proof of this; however, it had no impact on the dimethylation of H3K9 in the KsRE. Kisspeptin was shown to have a positive effect on transcriptional activation of the *GnRH* gene by facilitating the functional establishment of a chromatin loop between the KsRE and the downstream-located neuron-specific element; this was discovered by chromosome conformation capture analysis.[33]

In addition to influencing reproduction through epigenetic mechanisms,[34,35] kisspeptin neurons relay several environmental stimuli down the HPG axis and serve as an

intermediary in the sex-steroid-driven feedback mechanisms.[36] Toxins in the diet and the environment may have a significant impact on fertility by modulating the function of neurons that produce Kiss. The finest illustration of how epigenetics may be utilized to regulate a biological process such as puberty is provided by the NAD+-dependent deacetylase Sirtuin 1 (SIRT1), which genetically modifies Kiss1 expression in the hypothalamus.[37] SIRT1 works as a metabolic sensor that activates or represses gene expression via pathways of energy availability, molecules involved in transcription, and the deacetylation of histone proteins, all of which are essential for successful reproduction.[38]

The Onset of Puberty and GnRH Regulator

Among its many functions, kisspeptin is well recognized for guarding the entrance to puberty and regulating the release of pulsatile GnRH. The HPG axis is controlled by the GnRH neurons that are located in the basal forebrain. Axon terminals in the median eminence of the hypothalamus release pulsatile GnRH into the circulation of the hypophysis, which in turn triggers the pulsatile synthesis of LH and FSH.[39,40] These hormones aid in the growth of the testes and ovaries, allowing for the production of sperm and eggs. Even though negative or positive feedback from gonadal sex hormones on GnRH release is well documented, GnRH neurons lack estrogen receptors.[40] Since kisspeptin neurons in the anterior ventricular preoptic region (AVPP) are known to regulate GnRH neurons upstream, the observation that these neurons express estrogen receptor (ER2) suggests that estrogen regulates GnRH indirectly via kisspeptin.[41] Research on the role of kisspeptin in reproduction in animals has exploded thanks to the discovery of Kiss1's modulation of GnRH via sex steroids. Kiss1 mRNA is reported to grow significantly in the AVPV neurons of both male and female mice from juvenile to adulthood. Adult mouse GnRH neurons are stimulated by kisspeptin and become sensitive throughout postnatal development, although co-expression of the *Kiss1R* does not alter from juvenile to adulthood.[42] If the kisspeptin receptor is blocked or deleted during the juvenile period, puberty development is thrown off. The pulsatile GnRH and LH surge is entirely suppressed in male and female mice lacking *Kiss1*.[43]This demonstrates that Kiss-KissR's important function in generating GnRH pulses is crucial for puberty in mammals. It is known that the reproductive axis is driven by neurokinin-B, dynorphin A, and melanocortin, as well as by genetics, the environment, and peripheral cues; however, neither the cause nor the time of pubertal transition is well understood.[44,45] Numerous studies in animals, especially mice, demonstrate that kisspeptin is a potent secretagogue of hypothalamic GnRH, which governs the onset of puberty.[46]

Kisspeptin and Its Physiology

The reproductive system is controlled by a web of complex feedback loops between the hypothalamus and pituitary gland. In females, the ovaries play a pivotal role in controlling hormone levels through the hypothalamic-pituitary-ovarian axis. The pituitary gland secretes FSH and LH in response to pulsed hypothalamic release of GnRH, a mechanism known as the hypothalamic-pituitary axis.[47] Together, these gonadotropins have a synergistic effect on steroidogenesis in the ovaries. Pulsatile GnRH secretion is the primary regulator of reproductive processes. Regulation of GnRH occurs through both direct and indirect mechanisms. Neuropeptides and neurotransmitters, such as galanin, neuropeptide Y, neurokinin B (NKB), nesfatin-1, kisspeptin, corticotropin-releasing hormone, and norepinephrine, all have roles in modulating GnRH function, and many more.[48] Particularly, kisspeptin seems to play an important role in controlling fertility.

Several regions of the human brain, including the hippocampus, anterior pituitary gland, and hypothalamus (especially the infundibular nucleus), exhibit significant levels of KISS1R. Additionally, the pancreas, liver, ovaries, and adipose tissue all have high levels of KISS1R expression in addition to the brain.[9] Kisspeptin secretion and the complex mechanisms by which it acts are currently the subject of intensive study.

KNDy Neurons and Their Physiology in the Regulation of the Hypothalamic Reproductive System

The reproductive axis (hypothalamus-pituitary-ovarian axis) greatly depends on GnRH pulsatile generation. Most human neurons that produce GnRH are located in the hypothalamic infundibular nucleus; from the infundibular nucleus, these neurons travel to the median eminence.[49]

The pulsatile release of gonadotropins (FSH and LH) is stimulated by GnRH secretion from this anatomical location. Considerable progress has been made in studying the effect of kisspeptin on GnRH production since its discovery and identification in the hypothalamus. In the infundibular nucleus, KNDy neurons co-express the opioid peptides dynorphin (DYN), neurokinin B (NKB), and kisspeptin. The first known clusters of KNDy neurons were discovered in a sheep's brain in 2007.[50] Subsequent research in the human hypothalamus found anatomically similar clusters of neurons. Research has shown that KNDy neurons are critical for controlling GnRH neuron activity.[51] It has recently been discovered that NKB and DYN neurons regulate kisspeptin's effect on GnRH secretion.[52] Specifically, NKB is essential for starting kisspeptin pulses, which triggers GnRH secretion in the body. The release of kisspeptin is inhibited by DYN neurons, which reduces GnRH's pulsatility (Figure 2). KNDy neuron expression has been shown to be sex-specific. The researchers demonstrated the presence of KNDy cell populations and sexual dimorphism using immunohistochemistry and deep brain imaging; female participants had higher KNDy in the arcuate nucleus (ARC) than male specimens.[53] Not only do humans exhibit sexual dimorphism, but so do other primates and rodents. Understanding how ovarian sex steroids affect KNDy neuron function is critical for appreciating their larger purpose. KNDY neurons express a wide variety of receptors for steroid hormones, including NKB, DYN, estradiol receptors, and progesterone receptors. Because of this, the KNDy neuron can serve as the reproductive system's master integrator of systemic feedback.[54]

Thus, ovarian steroids can regulate *KISS1* expression in the hypothalamus. In turn, kisspeptin triggers the pulsatile release of GnRH. Ovarian steroid secretion during the early follicular phase can inhibit GnRH release; on the other hand, LH pulsatility might be triggered by increased estradiol

production during the late follicular phase, increasing GnRH release.[55,56]

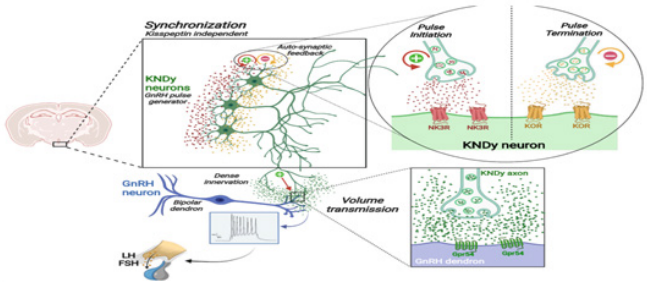

Fig. 2. *"KNDy neurons and GnRH pulse generation: a schematic overview of the fundamental processes. KNDy neurons, with their many collateral connections, create a highly interconnected network that coordinates the release of kisspeptin from GnRH neurons in order to generate GnRH pulses. When it comes to pulse formation, NKB is essential for starting kisspeptin pulses, whereas Dyn has the opposite effect and is in charge of stopping them. While entire GnRH pulses may be generated without kisspeptin input to GnRH cells, synchronization of KNDy neurons does need it. Transmission between KNDy neurons and GnRH dendrons near the edge of the median eminence is expected to take place through volume transmission, as shown by recent data."*[14]

Expression of Kiss1 mRNA in the rat ovary varies depending on the ovulatory increase in gonadal hormones,[56] peaking during the pre-ovulatory phase. Furthermore, when prostaglandin synthesis was inhibited, ovulatory dosages of human chorionic gonadotropin could not stimulate *Kiss1* expression in the rat ovary, which is known to greatly impair ovulation.[57] These results hinted, if indirectly, to a possible function for local kisspeptins in regulating ovulation. This theory is supported by the observation that anti-kisspeptin infused intra-ovarian decreased the quantity of corpus luteum, a marker of ovulation, but kisspeptin injected directly into the ovary had the opposite effect.[58] Kisspeptins have been found in clinical studies to promote egg maturation and ovulation in animals,[59] reduce the likelihood of developing ovarian hyper-stimulation syndrome, and promote oocyte maturation in high-risk individuals.[60] Parenteral injection of kisspeptin also produces substantial gonadotropin responses, making it challenging to disentangle the local and central mechanisms responsible for these results.

Taken together, these findings and evidence of Gpr54 expression in oocytes in rodent, canine, and porcine species reveal a potential role for kisspeptin's direct effects in regulating ovulation, a lack of which would lead to premature ovulatory failure, which is analogous to premature ovarian insufficiency (POI). However, there is insufficient evidence of whether kisspeptins act on oocytes directly or indirectly. Selective oocyte depletion of Gpr54 causes the progressive POI-like syndrome, manifesting as increased atresia of big antral follicles and early anovulation, but no effect on resting follicle numbers or development. [61]

Kiss1 and Kiss1R in Testis and Spermatozoa

Multiple types of signaling—autocrine, paracrine, and endocrine—contribute to the complex process of spermatogenesis. In the interstitium, Leydig cells create sex steroids, and growing germ cells get structure and nutrition from Sertoli cells.[62] This relies heavily on the coordinated proliferation and death of germ cells as well as the meiotic division and differentiation processes in which these cells play a central role. In mammalian and non-mammalian vertebrate testes, the kisspeptin system's location inside the testis, possible autocrine and paracrine activities, steroid synthesis, the development of sperm production, and sperm functions have all been studied.[63-65]

Blood levels of kisspeptin in males vary depending on their fertility, with levels being much greater in fertile males than in infertile ones.[66] In particular, people with HH have elevated plasma kisspeptin levels, but these levels decrease following GnRH replacement treatment because the hypothalamic sex-steroid feedback mechanisms have been restored.[67] Testicular Kiss1R signaling is essential for steroidogenesis; however, in patients with *KISS1R* inactivating mutation,[68,69] gonadotropin stimulation does not necessarily restore testosterone synthesis and spermatogenesis, similar to how *Kiss1R*-/- knockout animals still need an intra-testicular kisspeptin signal for spermatogenesis.[70] Spermatogenesis cannot be returned by activating the GnRH-secreting neuron and reactivating the Kiss1R gene. Male *Kiss*-/- mice with HH treated with testosterone had normal levels of plasma and intra-testicular testosterone and sustained spermatogenesis until sperm were produced that could fertilize eggs in vitro. Still, these animals were unable to inseminate females.[71] Kisspeptin can stimulate spermatogenesis in most intact animal models after being administered.[72-74] However, persistent overstimulation of the kisspeptin-dependent HPG axis leads to testis damage[75] and shuts off the HPG axis via desensitization of the Kiss1R in the testes.[76] It has been hypothesized that luteinizing hormone (LH)-dependent intra-testicular kisspeptin synthesis has a synergistic effect on postnatal testicular development and Leydig cell maturation in rats.[77] Kisspeptin is produced centrally and activates the HPG axis, which causes the hypothalamus to secrete GnRH and the anterior pituitary to produce gonadotropin LH. Kiss1 expression is upregulated by LH signaling in Leydig cells through cyclic adenosine monophosphate and protein kinase activation A pathway.[78,79] Effects on GnRH expression in Leydig cells in vitro have been documented, and the intra-testicular GnRH system, estradiol, and testosterone levels of non-mammalian vertebrates have been shown to be modulated.[73,80] Reports suggesting that kisspeptin affects the progression of spermatogenesis have been corroborated by recent investigations utilizing ex vivo testes explants and more physiological conditions, such as co-culturing germ and somatic cells.[72,73,80,81]

However, the importance of the intra-testicular kisspeptin system remains unclear and up for debate, although in vivo, ex vivo, and in vitro data suggest a possible role in Leydig cell function, steroid secretory activity, or spermatogenesis.[64] Goat, hamster, mouse, and rat epididymis have been defined, and the system is expressed in humans, bulls, rodents, and frogs.[65,82] However, the importance of kisspeptin in achieving spermatozoa (SPZ) competence for fertilization has not been thoroughly explored. Kiss1R is predominantly found in the post-equatorial area of the human brain[83] and the acrosomal region of the mouse brain.[84]

The kisspeptin system in SPZ can be controlled by specific agonists/antagonists under physiological conditions; however, this has only been described in human and mouse SPZ.[84] Human sperm hyper-motility was reported to be affected by kisspeptin-13.[83] However, kisspeptin-13 was found to affect the fertilization potential of rat SPZ obtained from the cauda epididymis.[84] Previous research studied the kisspeptin system in dog and rat SPZ,[82,85]) providing evidence of Kiss1R trafficking in SPZ head during the transit from caput to cauda epididymis.

Using a canine model that is somewhat close to humans, and using a combination of flow cytometry, epifluorescence microscopy, and Western blot on specific membrane protein fractions, scientists were able to identify Kiss1R on membrane-intact SPZ extracted from the epididymal tail. For instance, the presence of Kiss1R on the surface of SPZs coincides with the growth of protamination rate and motility, two characteristics of fully developed epidydimal cells.[85] From the caput's posterior SPZ head region, Kiss1R travels to the tail's perforatorium, as shown by an analysis of permeabilized SPZ from the caput and tail epididymis of rats.

Kiss1 was detected in canine and rat epididymal fluid using a dot blot assay.[82] High levels of Kiss1 were detected in the epididymal fluid and plasma of rats using a more sensitive ELISA technique, which served as a positive control.[82] Kiss1R trafficking is considered to be a hallmark of proper sperm production, and kisspeptin signaling may be a signal for SPZ storage in the epididymis. The lack of functional data on the activity of Kiss1R in SPZ acquired from different epididymal tracts in both healthy and pathological situations is a significant drawback of the previous research and requires more study. Kisspeptin levels in the seminal plasma were positively associated with sperm quality in a large sample of healthy males, according to the study's authors. The concentration of kisspeptin in seminal plasma was much greater than that in blood plasma. The occurrence of SPZ problems in animal models suggests that measuring kisspeptin levels in the seminal plasma of normal-spermic, sub-fertile, and infertile males and SPZ-deficient animals may be interesting.

Kisspeptin Analogs

Kisspeptin Agonists

There has been a rise in the use of kisspeptin analogs to treat endocrine diseases. Kisspeptin agonists are most useful in assisted reproductive technologies for inducing ovulation. Couples struggling with infertility may be hesitant to try IVF because of the risk of serious complications, such as OHSS.[86] The complications of OHSS include kidney failure, acute respiratory distress syndrome, swollen ovaries, and even death.[87] Medication used to promote ovulation for oocyte extraction in IVF regimens is the primary cause of OHSS.[88,89]

In this aspect, kisspeptin may be a more secure option than current IVF protocols. Ovulation necessitates kisspeptin due to its role in stimulating the preovulatory LH surge. In women undergoing IVF, kisspeptin analogs (such as kisspeptin-54) have been shown to be effective in stimulating oocyte maturation. The delivery of kisspeptin-54 resulted in egg maturation in a study by Jayasena et al.[90] The average number of developed eggs per patient is also associated positively with the amount of analog given to each individual.[90] The conventional medicines used to stimulate oocyte maturation were compared to kisspeptin-54 in a head-to-head trial conducted by Owens et al.[91] Serum levels of FSH and LH measured after the kisspeptin administration were more suggestive of a normal hormonal cycle than those measured after administering conventional medications. Abbara et al.[60] found that while the LH surge following the kisspeptin administration is smaller than that of a standard GnRH agonist, it may increase oocyte maturation by acting on kisspeptin receptors in the ovaries. Abbara et al.[92] also gave kisspeptin-54 to 60 women at high risk of OHSS to test the hormone's capacity to stimulate oocyte maturation in preparation for in vitro fertilization. Ninety-five percent of treated women matured their oocytes, and no women had mild, moderate, or severe OHSS. In women who are at high risk of OHSS, this finding supports the use of kisspeptin-54 to stimulate oocyte maturation during IVF. Beyond *their* use to stimulate ovulation, kisspeptin agonists provide promise in the treatment of people with disorders linked with decreased LH output. Plasma levels of luteinizing hormone have been studied by Whitlock et al.,[93] who investigated the effects of kisspeptin and kisspeptin receptor agonists. Serum LH levels in sheep increased significantly after treatment of both. Kisspeptin agonists may be useful in treating illnesses such as hypothalamic amenorrhea; according to these findings, women who suffer from functional hypothalamic amenorrhea may benefit from receiving an intravenous infusion of kisspeptin-54 since it has been shown to boost LH pulsatility. This paves the way for additional research into the efficacy of kisspeptin-based treatments in treating functional hypothalamic amenorrhea in females.[94] Kisspeptin was also studied in relation to pubescence; prepubertal bull calves were given analogs of kisspeptin, as well as acute and subacute doses of kisspeptin, and both methods of administering kisspeptin analogs were linked to increases in LH levels. However, subacute treatment of a kisspeptin analog led to lower levels of the hormone FSH. Subacute treatment of a kisspeptin analog has been shown to reduce FSH levels, suggesting that this approach may be effective for controlling puberty onset.[95]

Kisspeptin Antagonists

Administering drugs that block kisspeptin's effects on the hypothalamus, pituitary, and ovary was a key step in elucidating the hormone's physiological role. The administration of peptide-234, a potent kisspeptin antagonist, decreases the mean GnRH concentration and inhibits spontaneous GnRH pulses in Rhesus monkeys. It was also shown to reduce LH pulses in ovariectomized sheep.[96] Antagonists of kisspeptin have shown promise and may find use in clinical practice. The most obvious use is in the treatment of patients with polycystic ovary syndrome (PCOS), postmenopausal symptoms, or early onset puberty,[97] all of which are associated with elevated LH concentrations. Peptide-234 infusions have been demonstrated to suppress reproductive organ growth in reproductive-age female rats. Even though there was no impact on BMI, the onset of pubertal milestones, such vaginal opening was also delayed.[98] Kisspeptin and neurokinin B antagonists may normalize GnRH production, lowering LH concentrations in PCOS women. In turn, this would boost oocyte maturation and revive folliculogenesis. GnRH and LH pulses are both elevated

in postmenopausal and PCOS women. Therefore, a kisspeptin antagonist may be helpful for women experiencing vasomotor symptoms during and after the menopause transition.[99] Currently, GnRH analogs are the sole medicine used to treat premature puberty. Mutations in the KISS1 and KISS1R genes have been linked to early-onset puberty.[100] Inhibiting pubertal growth using kisspeptin antagonists has been demonstrated in animal models of precocious puberty. The growing body of evidence and increasing understanding of kisspeptin's actions suggest that it may one day serve as a therapy alternative for this population of patients.

Conclusion

The growing body of evidence implicating kisspeptin as a crucial factor in aiding the start of puberty and establishing reproductive functions in animals strongly shows that kisspeptin plays a fundamental role in reproductive regulation. Additionally, it is essential in controlling the hypothalamic-pituitary-gonadal axis. Activities such as steroidogenesis, follicular development, ovulation, and ovarian senescence are all influenced by kisspeptin activity. For many people with infertility, the peptide hormone kisspeptin represents a ray of hope.

Competing Interests

The author declared that there are no competing interests.

Acknowledgments

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