Journal of MTU 2024;3(1):31-39
ISSN: 2822-4094

Review Article / Derleme Makalesi

Journal of Medical Topics & Updates (Journal of MTU)

Doi: 10.58651/jomtu.1454284

The role of kisspeptin in female and male reproduction

Dişi ve erkek üreme sisteminde kisspeptinin rolü

Oya KORKMAZ

Department of Histology and Embryology, School of Medicine, Malatya Turgut Ozal University, Malatya, Türkiye.

ABSTRACT

Kisspeptin is a neuropeptide responsible for controlling the synthesis of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The G-protein-coupled receptor 54/kisspeptin 1 receptor (GPR54/KISS1R) is involved in its action. The comprehension of kisspeptin and its actions represents a significant breakthrough in the field of reproductive biology. Kisspeptins play a crucial role in the development and optimal functioning of the reproductive system in both female and male. Additionally, it contributes to the onset of puberty, regulating feedback processes, and influencing sexual desire and arousal. It regulates a number of reproductive functions in women, including ovulation, lactation, ovarian development, follicle development, oocyte maturation, and pregnancy via the hypothalamic-pituitary-gonadal (HPG) axis. Spermatogenesis, sperm function, Leydig cells, and reproductive behaviour are all impacted by it in men. Infertility and polycystic ovarian syndrome (PCOS) are among the diseases linked to kisspeptin dysregulation, according to the research. For potential future use in diagnosing and treating problems, it may be helpful to understand the mechanisms behind kisspeptin's effects on the reproductive system. This review focuses on the regulatory function of kisspeptin on the HPG axis and the impact of kisspeptin on reproductive processes in both female and male.

Keywords: Kisspeptin, HPG axis, Reproduction, Infertility

ÖZET

Kisspeptin, gonadotropin salgılatıcı hormon (GnRH), lüteinizan hormon (LH) ve folikül uyarıcı hormon (FSH) sentezini kontrol etmekten sorumlu bir nöropeptittir. Etkilerini G-protein-bağlı reseptör 54/kisspeptin 1 reseptörü (GPR54/KISS1R) olarak bilinen G-protein-bağlı bir reseptör aracılığıyla göstermektedir. Kisspeptin ve etkilerinin anlaşılması, üreme biyolojisi alanında önemli bir atılımı temsil etmektedir. Kisspeptinler hem erkeklerde hem de kadınlarda üreme sisteminin gelişiminde ve optimal işleyişinde çok önemli bir rol oynamaktadır. Ayrıca ergenliğin başlamasında, geri bildirim süreçlerinin düzenlenmesinde ve cinsel istek ve uyarılmayı etkilemede görev almaktadır. Kadın üreme sisteminde, HPG ekseni aracılığıyla gebelik, emzirme, yumurtalık gelişimi, folikül gelişimi, oosit olgunlaşması ve yumurtlama gibi çeşitli süreçleri kontrol etmektedir. Erkek üreme sisteminde ise Leydig hücreleri, spermatogenez, sperm fonksiyonu ve üreme davranışının düzenlenmesinde rol oynamaktadır. Araştırmalar, polikistik over sendromu (PCOS) ve infertilite gibi durumlarda kisspeptin düzensizliğinin patojenik önemini ortaya koymuştur. Kisspeptinin üreme ekseni üzerindeki etkisi ve ilişkili mekanizmaları hakkında fikir edinmek, kisspeptinin gelecekte hastalıkların tanı ve tedavisinde kullanılmasını kolaylaştıracaktır. Bu derleme, kisspeptinin hipotalamik-hipofiz-gonadal (HPG) eksen üzerindeki düzenleyici işlevine ve kisspeptinin hem kadınlarda hem de erkeklerde üreme süreçleri üzerindeki etkisine odaklanmaktadır.

Anahtar Kelimeler: Kisspeptin, HPG ekseni, Üreme, İnfertilite

Geliş Tarihi / Received: 17.03.2024, Kabul Tarihi / Accepted: 30.03.2024
Sorumlu Yazar / Corresponding Author: Oya KORKMAZ, Malatya Turgut Ozal University, School of Medicine, Basic Medical Sciences, Deparment of Histology and Embryology, Malatya,Türkiye. e-mail: oya.korkmaz@ozal.edu.tr

INTRODUCTION

Every species relies on its reproductive capabilities to stay alive. An important part of reproductive regulation in humans and other animals is the hypothalamic-pituitary-gonadal (HPG) axis, which comprises the anterior hypothalamus, pituitary gland, and gonads. The HPG axis has a major impact on ovulation, spermatogenesis, oocyte maturation, follicle growth in females, and other male reproductive processes. Neurons responsible for generating gonadotropin-releasing hormone (GnRH) transmit projections to the median eminence when they establish connections with their neural network. This occurs after the neurons have travelled to the medial preoptic area, where they serve as the promoters of the HPG axis. The pituitary gland in all animals is responsible for the release of gonadotropins, and these cells are the final output cells of the neural network that governs this process. On the other hand, it is common knowledge that GnRH neurons do not possess oestrogen receptors α or progesterone receptors. This observation implies that the mechanisms by which oestrogen and progesterone influence the gonadal axis via negative and positive feedback are not directly mediated by GnRH neurons but rather by other neuronal subtypes.

The neuropeptide kisspeptin was first identified by Lee et al. in 1996 (Lee et al., 1996). It was eventually discovered that it exerts its effects by way of the G-protein-coupled receptor, also known as GPR54. Seminara et al. (2003) and Gottsch et al. (2004) provided evidence that kisspeptins have a direct impact on reproduction through their regulation of GnRH secretion; thus, they are essential regulators of the HPG axis (Seminara et al., 2003, Gottsch et al., 2004) (Figure 1). Kisspeptins were initially thought to be associated with cancer metastasis; however, it was subsequently shown that they are closely tied to reproduction too. In humans, the term "kisspeptin" refers to a class of neuropeptides that are produced by the cleavage of a precursor peptide that is 145 amino acids long and is encoded by the Kiss1 gene system. Although it is believed that kisspeptin is primarily active as a peptide consisting of 54 amino acids, it is found in mice as a peptide consisting of 52 amino acids. It has been found that the location of kisspeptin neurons in rats and humans is actually different. Research on rodents proved that kisspeptin neurons are located in the arcuate nucleus and the anteroventral periventricular nucleus, which extends into the periventricular nucleus (Figure 1). The last two nuclei, often called the rostral nuclei, are located in the rostral periventricular region of the third ventricle. Kisspeptin neurons were found to be mostly located in the infundibular nucleus of human brains, with a small number of them also being found in the preoptic region. In addition to these locations, kisspeptin can also be found in the paralimbic and limbic regions of the brain, as well as in extra-hypothalamic regions, as well as in the placenta, testes, pancreas, ovary, liver, and small intestine, which are located in peripheral areas (Ohtaki et al., 2001; Muir et al., 2001; Kotani et al., 2001; Clarkson et al., 2006; Gaytán et al., 2009).

An orphan receptor called Kiss1R was found in the brain of a rat. The 398-amino-acid Kiss1R protein is found in the cerebellum, pons-medulla, cerebral cortex, and thalamus in the human brain, and it is encoded on chromosome 19p13.3. Several organs in the human body have Kiss1R mRNA. These tissues include the stomach, pancreas, thymus, spleen, small intestine, lung, gonads, and many more (Ohtaki et al., 2001; Muir et al., 2001). According to Hu et al. (2018), Kiss1R is expressed in the theca, granulosa, epithelial, and stromal cells of the human ovary (Hu et al., 2018). Kiss1R is also found in placental trophoblasts and in human endometrial stromal cells, which is another interesting finding (Wu et al., 2014; Baba et al., 2015). In addition, the fact that mutations that are associated with the kisspeptin pathway have the potential to cause reproductive issues lends further credence to this effect. There are physiological and pathological functions for kisspeptin and kiss1R. They have a role in disorders like polycystic ovarian syndrome (PCOS) and infertility due to prolactinoma-induced hyperprolactinemia (Chanson et al., 2019). Furthermore, researchers are also investigating the role of kisspeptin and related neuropeptides in influencing sexual behaviour and desires, which may ultimately impact libido (Harter et al., 2018). In line with this information, it can be said that Kisspeptin and Kiss1R have recently played a very important role in the reproductive system.

Since the initial revelation of the relationship between reproduction and kisspeptin, research on this topic has progressed rapidly. It is crucial to understand the regulatory role and specific mechanisms of kisspeptin in the HPG axis. This review specifically examines the regulatory role of kisspeptin on the HPG axis and its effects on reproductive processes in both female and male.

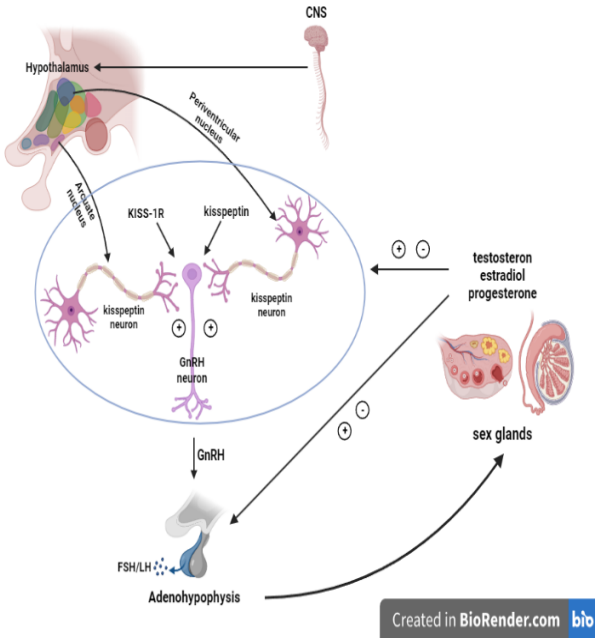

Figure 1. The organisation of the hypothalamic-pituitary-gonadal axis and its control by kisspeptin. Note: The symbol "-" represents negative feedback, whereas the symbol "+" represents positive feedback.

Effect Of Kisspeptin On Female Reproduction

The hypothalamic–pituitary–ovarian axis is responsible for a significant amount of the regulation of female reproduction. A direct connection exists between the ovary and the maturation of follicles, the process of ovulation, the production of the corpus luteum, and the secretion of steroid hormones. Because it is a crucial regulator, kisspeptin influences female reproduction in a number of different ways. These include the secretion of gonadotropin, the development of follicles, the maturation of oocytes, and the process of ovulation (Figure 2).

The Role Of Kisspeptin In Follicular Development

Kisspeptin levels in humans increase as the phase changes from the early follicular to the preovulatory. By downregulating FSHR expression, kisspeptin influences follicular growth and the recruitment of primary and secondary follicles, as demonstrated by Fernandois et al. (2016) (Fernandois et al., 2016). Direct administration of kisspeptin into the ovary resulted in a reduction in the overall count of antral follicles, including those that were atretic, in rats aged 6 and 10 months. Conversely, the application of the KissR antagonist p234 had the opposite effect. In a laboratory experiment conducted outside of a living organism, kisspeptin acts as a functional antagonist by preventing the rise in FSHR expression caused by ISO, which is α β-adrenergic agonist. Another important dimeric glycoprotein that regulates follicle development is kisspeptin, which can enhance serum anti-Müllerian hormone (AMH) synthesis. AMH, synthesised by preantral and small antral follicles, controls the selection of primordial follicles and modifies the sensitivity of follicles to follicle stimulating hormone (FSH) (Dewailly et al., 2014; Fleming et al., 2020). The study observed an elevation in blood AMH levels following the local injection of kisspeptin, while a decline was observed after the use of p234 in rats aged 6 and 10 months. In summary, kisspeptin has the potential to impede the growth of preantral follicles in the ovary by increasing the production of AMH and reducing the expression of FSHR.

The Role Of Kisspeptin In Oocyte Maturation

The preovulatory LH surge is widely acknowledged to trigger the transition from meiosis to metaphase II and vice versa in each reproductive cycle. Also, in porcine cumulus-oocyte complexes (COCs), scientists have looked at how kisspeptin affects oocyte development. According to Saadeldin et al. (2012), the addition of kisspeptin to porcine COCs in vitro stimulates the maturation of oocytes, which means that kisspeptin acts directly on oocytes (Saadeldin et al., 2012). As to the research conducted by Persani et al. (2014), one possible mechanism could be a rise in the levels of C-MOS, GDF-9, and BMP-15 (Persani et al., 2014). C-MOS has a crucial role in activating several processes that take place during oocyte development. These processes include the meiotic process, the creation of normal spindles and chromosomes, and the reactivation of purified maturation-promoting factors following the first meiotic phase. In addition, GDF-9 and BMP-15 play a role in the regulation of a variety of physiological processes, including the maturation of oocytes, the formation of follicles, ovulation, and luteinization (Persani et al., 2014; McNatty et al., 2005).

Cumulus granulosa cells, often known as GCs, have been discovered to play a significant role in the process of regulating the maturation of oocytes. Chakravarthi et al. (2021) observed a notable abundance of kisspeptin in granulosa cells (GCs) treated with gonadotropin, while KissR was found in oocytes (Chakravarthi et al., 2021). This discovery indicates that kisspeptin produced from the gonadotropin-releasing hormone receptor may directly affect the maturation of oocytes by interacting with the Kiss1R receptor using the mitogen-activated protein kinase (MAPK) signalling pathway (Chakravarthi et al., 2021; Mottershead et al., 2012). Given the absence of kisspeptin expression in GCs of ERβ knockout rat ovaries, it may be inferred that the expression of kisspeptin in GCs relies on the presence of the oestrogen receptor β (ERβ).

Chakravarthi et al. (2021) found that the application of kisspeptin can enhance the development of oocytes lacking cumulus cells in both wild-type and ERβ^{null} rats (Chakravarthi et al., 2021). This conclusion is in line with the findings that were presented earlier. Therefore, kisspeptin may have an effect on oocytes that is both autocrine and paracrine, and it may be something that is both persistent and direct.

The Role Of Kisspeptin In Ovulation

The process of ovulation is a complex one that is characterised by the rupture of the follicle and the release of the oocytes. This process is mediated by the surge of the luteinizing hormone (LH) and is controlled by a number of unique genes. According to Zeydabadi et al. (2017), high levels of oestrogen have an effect on anteroventral periventricular nucleus kisspeptin neurons near the end of the follicular phase (Zeydabadi et al., 2017). This action causes the release of kisspeptin, which in turn causes a cascade of events that culminate in ovulation, a surge in GnRH, and even a peak in LH. According to Sirois et al. (2004), the functions of the LH peak are successfully accomplished by the upregulation of cyclooxygenase-2 (COX-2) and the production of prostaglandin (Sirois et al., 2004). Peripheral delivery of kisspeptin has been shown to promote ovulation in a variety of species, including rats (Matsui et al., 2004) and sheep (Caraty et al., 2007). This has been demonstrated through research. Kisspeptin's influence on ovulation is primarily accomplished by elevating levels of both FSH and LH. Subcutaneous administration of kisspeptin to 25-day-old female rats resulted in a considerable increase in plasma levels of FSH and LH (Matsui et al., 2004). Trevisan et al. (2018) found that the LH pulses in human volunteers increased considerably right after they were given kisspeptin-10 (Trevisan et al., 2018). Through the stimulation of precisely timed endogenous LH release that was constant in both amplitude and duration, Kisspeptin-54 was able to induce ovulation in mice (Owen et al., 2021). Cao et al. (2019) found that rats may have impaired ovulation if given a COX-2 inhibitor or a COX non-selective inhibitor, which may reduce levels of ovarian Kiss1 mRNA (Cao et al., 2019). This suggests that elevated COX-2 levels may affect kisspeptin expression levels, which in turn promote appropriate LH levels.

In Kiss1R mutant mice, conventional gonadotropin priming was able to induce ovulation (Seminara et al., 2003). This indicates that ovarian kisspeptin signalling is unnecessary for the process of ovulation. Therefore, contrary to initial expectations, the importance of ovarian kisspeptin during ovulation may not be as great.

However, while the oocyte quality in mice lacking Kiss1 and Kiss1R specific to neurons is comparable to that of wild-type mice, the knockout animals displayed a significantly diminished number of ovulated oocytes and corpora lutea. Gaytan et al. (2014) found that the simultaneous stimulation of GnRH and gonadotropin is not enough to repair the loss of function caused by the deletion of Kiss1R (Gaytan et al., 2014).

Kisspeptin And Male Reproduction

Both in terms of their central and peripheral effects, kisspeptin's actions in males are equivalent to those in females (Figure 2). This is true for both central and peripheral effects. During the primary activity, it exerts its impact on the GnRH neurons situated in the hypothalamus. As a result, it stimulates the secretion of GnRH, which in turn leads to the generation of LH and FSH. Men who have a mutation or deletion in the Kiss1R gene have been shown to be at risk of developing hypogonadotropic hypogonadism. This has been established through research. It is a component of the peripheral action that has an effect on the testicles, which it exerts its influence on. Both the presence of Kiss1 in human testes and the activity of this protein have been demonstrated by a number of investigations that have been conducted. Simply depending on the central action alone is inadequate; the concurrent effects on the hypothalamus and testes also contribute to promoting the normal functioning of the reproductive system. The reproductive system is responsible for creating and maintaining the reproductive system. Research has shown that kisspeptin has a direct influence on the male gamete, leading to the existence of data supporting this hypothesis. The presence of Kiss1R in specific regions of human spermatozoa, such as the head (post-acrosomal area), flagellum, and neck, provides evidence supporting the accuracy of the above assertion (Sharma et al., 2020). In seminal plasma, there is an additional distribution of Kiss1, as observed in reference (Sharma et al., 2020). Furthermore, kisspeptin not only leads to a boost in sperm motility, but also triggers a brief surge in sperm hyperactivation. This effect is achieved through an elevation in intracellular calcium levels within the sperm cells (Sharma et al., 2020). As a result of this, kisspeptin has a significant impact on sperm activity. A recent study conducted by Zou et al. (2019) examined a group of 666 Chinese students who willingly participated. The study found a positive correlation between the overall seminal plasma kisspeptin levels and the quality of sperm. The evaluation of sperm quality was conducted by considering parameters such as sperm concentration, total sperm count, and motile sperm count (Zou et al., 2019).

Spermatogenesis is a complex process that is continuously controlled by the autocrine, paracrine, and endocrine pathways in a sequential manner. It is crucial to maintain order among the functions of Leydig cells in the interstitium, Sertoli cells in the seminiferous tubules, meiotic division and differentiation, and germ cell proliferation and mortality. Sex-steroids are generated by Leydig cells, whereas developing germ cells receive structural and nutritional support from Sertoli cells. The presence and characteristics of the kisspeptin system in the testes of both mammalian and non-mammalian vertebrates have been detected and described. These findings have uncovered potential activities in local communication within the testes, the production of steroids, the advancement of sperm development, and the functioning of sperm cells (Sharma et al., 2020; Chianese et al., 2016; Meccariello et al., 2020). Nevertheless, there are variations in the specific distribution of the kisspeptin system among different species, which in turn may result in diverse activities.

Kisspeptin has been detected and measured in human plasma across various health conditions (Trevisan et al., 2018). A link exists between the reproductive status of males and the levels of circulating kisspeptin. Fertile men have significantly higher levels of kisspeptin compared to infertile men (Ramzan et al., 2015). Conversely, following the administration of GnRH replacement medicine, the levels of kisspeptin in the bloodstream decrease due to the reestablished sex-steroid feedback systems in the hypothalamus (Kotani et al., 2014). Some people with hypogonadotropic hypogonadism exhibit elevated amounts of kisspeptin in their plasma. Despite this, in clinical cases of Kiss1R inactivating mutations, gonadotropin stimulation to restore testosterone synthesis and spermatogenesis may not always be effective (Semple et al., 2005; Nimri et al. 2011). This indicates that the signalling of Kiss1R in the testicles is essential for the production of steroids. León et al. (2016) found that selectively reactivating the Kiss1R gene in the GnRH-secreting neuron of $Kiss1R^{-/-}$ knockout mice did not lead to the restoration of spermatogenesis (León et al., 2016). This further substantiates the critical significance of the intratesticular kisspeptin signal in facilitating the effective advancement of spermatogenesis. However, testosterone replacement in $Kiss^{-/-}$ mice who exhibit hypogonadotropic hypogonadism is able to restore plasma and intratesticular testosterone levels, as well as maintain spermatogenesis until the formation of sperm that are capable of fertilising oocytes in vitro. However, the mice that were treated with testosterone did not have the ability to impregnate females, as stated by Goto et al. (2020) (Goto et al., 2020).

According to Chianese et al. (2013) and Chianese et al. (2015), the injection of kisspeptin typically stimulates the process of spermatogenesis in animal models that are still intact (Chianese et al., 2013; Chianese et al., 2015). However, if the kisspeptin-dependent overstimulation of the HPG axis continues for a long time, it might cause harm to the testis (Ramzan et al., 2011). Additionally, the desensitisation of the Kiss1R receptor can turn off the HPG axis (Seminara et al., 2006).

Kisspeptin signalling is essential for both the maturation of Leydig cells and the development of the postnatal testis. The research conducted on rodents postulated the idea of synergistic effects involving the hypothalamus and LH-dependent intratesticular synthesis of kisspeptin. Kisspeptin, which is produced within the central nervous system, induces the secretion of GnRH from the hypothalamus and LH from the anterior pituitary gland via stimulation of the HPG axis. Leydig cells are activated by LH, leading to the increase in Kiss1 expression through the activation of the protein kinase A (PKA) pathway and cyclic adenosine monophosphate (cAMP). Furthermore, in vitro studies have reported documented occurrences of observed effects on the expression of GnRH in Leydig cells (Petrucci et al., 2020). In addition, it has been observed that the intratesticular GnRH system, as well as the levels of estradiol and testosterone, undergo changes in non-mammalian vertebrates (Chianese et al., 2015; Chianese et al., 2017). The co-cultivation of germ cells and somatic cells has recently unveiled the existence of kisspeptin-dependent influences on the progression of spermatogenesis (Toolee et al., 2019). These results complement observations made using ex vivo testes explants, which simulate more physiological settings (Chianese et al., 2013; Chianese et al., 2015; Chianese et al., 2017). As a result, although in vivo, ex vivo, and in vitro investigations have demonstrated that the kisspeptin system potentially influences the steroid secretion activity and the physiology of Leydig cells, as well as the progression of spermatogenesis (Meccariello et al., 2020), the precise nature of this relationship remains unknown and is the subject of ongoing debate (Sharma et al., 2020).

Kiss1R is primarily located in the post-equatorial segment in humans (Pinto et al., 2012), whereas it is primarily located in the acrosomic region in mice (Hsu et al., 2014). This is a difference in the localization of Kiss1R in each species. As of now, only mouse and human spermatozoa have undergone descriptions of the modulation of kisspeptin in epididymal spermatozoa induced by the presence of specific antagonists and agonists under physiological conditions (Pinto et al., 2012; Hsu et al., 2014). An inquiry was carried out to examine the fertilising capacity of mouse epididymal spermatozoa obtained from the epididymal tail in

response to the inhibition of Kiss1R by Kp-234 (Hsu et al., 2014). Furthermore, the impact of Kp-13 on the increased movement of human sperm was evaluated. According to Gloria et al. (2021), the presence of Kiss1R on the surface of the epididymal spermatozoa is parallel to the acquisition of the usual characteristics that are necessary for successful epidydimal development (Gloria et al., 2021). These characteristics include the rate of protamination and motility. An immunofluorescence analysis was performed on permeabilized epididymal spermatozoa isolated from the caput and tail epididymis of the rat. The results indicated that Kiss1R moves towards the posterior region of the head of the epididymal spermatozoa in the epididymal caput, and then migrates towards the perforatorium in the epididymal tail (Mele et al., 2022). The dot-blot assay successfully detected the presence of Kiss1 in the epididymal fluid of both canines and rodents (Gloria et al., 2021; Mele et al., 2022). A unique ELISA technique was employed to quantify significant amounts of Kiss1 in both the plasma (used as a positive control) and the epididymal fluid of rats (Mele et al., 2022). Hence, Kiss1R trafficking seems to serve as an indicator of complete sperm maturation, whereas Kisspeptin signalling potentially communicates the storage of epididymal spermatozoa in the epididymis. Both of these are important for the development of healthy sperm. Numerous healthy males were requested to have their seminal plasma and blood plasma kisspeptin levels measured. Kisspeptin levels were higher in seminal plasma than in blood, and higher kisspeptin levels were associated with better sperm (Zou et al., 2019). Therefore, it is worthwhile to investigate the kisspeptin system in animal models with a deficiency in epididymal spermatozoa, as well as in the seminal plasma of normospermic, subfertile, and infertile men, as an additional criterion for assessing sperm quality.

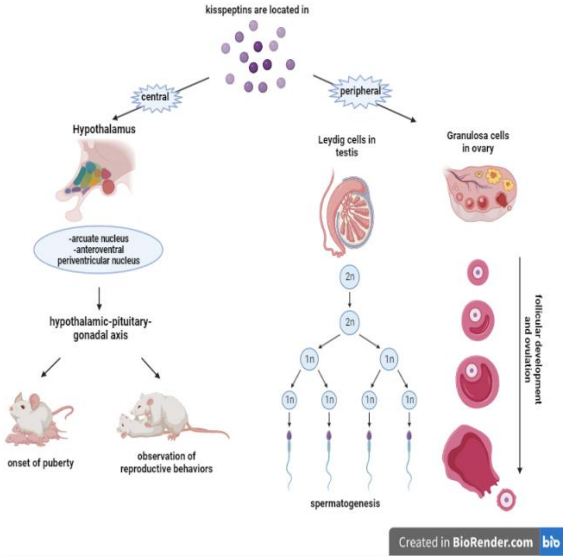

Figure 2. The reproductive function of kisspeptin and its distribution in the central and peripheral nervous systems

CONCLUSION

Kisspeptin is synthesised in the arcuate and periventricular nuclei of the hypothalamus, namely in the third ventricle. It also stimulates GnRH synthesis via Kiss1R. Kisspeptin helps with puberty, feedback processes, sperm quality, sexual impulses, pregnancy, the ovum, and lactation. Both the testes and ovaries produce steroids. Both mechanisms involve kisspeptin. Kisspeptin modulates the reproductive axis, spanning from the hypothalamus to the ovary, and facilitates ovulation and oocyte formation. Kisspeptin's role in steroidogenesis, sperm function, and reproductive behaviours is unclear, despite many advances in female and male reproduction. Kisspeptin's diagnostic and therapeutic uses must be studied to improve human reproductive health.

Acknowledgement: None

Ethics Committee Approval: Ethics committee approval is not required for this study.

Financial Resource/Sponsor's Role: No financial support was received for the study.

Conflict of Interest: There is no conflict of interest.

Author Contributions

Idea/Concept; Design; Supervision/Consulting; Data Collection and/or Processing; Analysis and/or Interpretation; Literature Review; Writing of the Article; Critical Review; Resources and Funding; Oya Korkmaz.

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