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KISSPEPTIN: A TEEN GENE ROLE BEYOND THE BRAIN

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ABSTRACT:

Kisspeptin gene is principal regulator for secretion of gonadotropin releasing hormone from hypothalamus, critical for puberty onset. Anteroventral and arcuate periventricular nuclei of hypothalamus express kisspeptin and their receptors. Kisspeptin's with **KISS1R** causes changes in hypothalamus cells by turning on phospholipase C. Countless studies have manifested KISS signalling system in numerous peripheral sites linking to biological processes, including regulation of pubertal onset, follicular development, oocyte maturation, ovulation, pregnancy, IVF treatment, lactation, testicular tissues, spermatogenesis, testicular steroidogenesis, pancreas and glucose metabolism, angiogenesis, liver and kidney functions. Researchers found various mechanism, pathology of Kisspeptin other than brain system using **KISS1** and **KISSR** lacking animals. This review gives insights of above discussed contents, its physiological functions outside the brain. Also, future aspects of Kisspeptin gene.

KEY WORDS: Kisspeptin, KISS1 gene, KISSR, hypothalamus, LH, FSH, POA, AVPV.

1.INTRODUCTION

Kisspeptin pulsatility (and subsequently **GnRH** pulses) must develop for sexual maturation to occur. In the fourteen years since its discovery, kisspeptin has come to prominence as an essential regulator of the HPG axis, which has addressed several issues connecting the regulation of reproductive hormone output from the hypothalamus. Persons with kisspeptin and kisspeptin receptor **(KISS1 or KISS1R)** inactivating mutations do not experience the onset of puberty, whereas activating mutations of KISS1R10 result in precocious puberty. By altering kisspeptin output onto **GnRH** neurons, external stimuli can hasten or delay the timing of the onset of puberty.[1] Because female reproduction carries a heavier energy burden than male reproduction, this regulation is essential for the longevity of the species. Further interest in the area has been sparked by the related revelation

that neurokinin B has a reproductive function. Kisspeptin and Neurokinin B are secreted by the same functional neural network; these neurons are now referred to as Kisspeptin-Neurokinin B-Dynorphin (KNDy) neurones because also secrete dynorphin, a well-known opioid inhibitor.[2] A small number of patients and healthy volunteers have received exogenous kisspeptin in an effort to restore reproductive function under certain conditions.[3]

2.ROLE OF KISSPEPTIN IN FEMALE REPRODUCTION:

2.1 Kisspeptin regulates pubertal onset

In 2001, researchers identified a new peptide called kisspeptin as an endogenous ligand of the orphan G-protein coupled receptor GPR54.[4-5] Clinical research later demonstrated that hyposecretion of gonadotropins, or hypogonadotropic hypogonadism, was a result of inactivating mutations of the GPR54 gene, which impaired pubertal maturation and reproductive functioning in humans.[6-7] Puberty onset is characterized by pulsatile release of **GnRH** with downstream effect on pituitary gonadotropin secreting cells via G protein-coupled receptor leading to pulsatile **LH** and **FSH** release.[8] The hypothalamus releases **GnRH** in a pulse-like pattern at the beginning of puberty, which is the result of a few excitatory and inhibitory mechanisms, plays a significant role at the onset of puberty. **GABA** and opioid peptide, for instance, are inhibitory factors while catecholamines and glutamate are excitatory factors.[9] Although the expression of **KISS1R** mRNA does not vary considerably in mice, it significantly rises in humans when they transit from juvenile to adult in **AVPV**. The stages involved in the mechanism are lowering EED and Cbx7, detaching Polycomb group, and transmitting Trithorax group elements to the Kiss1 promoter. This process ultimately leads to an increase in Kiss1 transcription. In females, the pubertal period's delayed growth of the **POA** kisspeptin neuron projection to the **GnRH** neuron cell body causes the **GnRH** surge, which causes the **LH** surge and the first ovulation.[9]

2.2 Kisspeptin in follicular phase

Periodically, at the midpoint of the menstrual cycle, a large release of gonadotropins known as the preovulatory surge occurs to cause ovulation in adult females. The ovarian pool's (ovarian reserve) primordial follicles, which were established early in life, are selected and activated to supply all developing follicles, including ovulated oocytes and primary, secondary, small, and large antral follicles. The spike style of GnRH secretion fuels this critical stage in female reproduction, in which rising quantities of **GnRH** are found in the portal circulation over a period of hours. Women experience preovulatory GnRH surges in the latter follicular phase of the menstrual cycle, which corresponds to the afternoon of proestrus in rodents (i.e., the period before ovulation at estrus). In order to generate this Preovulatory surge, there must be a change from the predominately negative feedback of oestrogen to the positively feedback of oestrogen, in which the rising levels of circulating **E2** from the dominant follicles send a signal to the **GnRH** neurons to stimulate rather than supressing **GnRH** secretion.[10] In rodent studies, it was shown that, while oestrogen suppresses Kiss1 mRNA levels in the **ARC**, the expression of the Kiss1 gene was decreased by ovariectomy and increased by oestrogen replacement in the **AVPV** which is located in the more rostral section of the hypothalamus. This was the first evidence for a putative role for Kiss1 neurons

in oestrogen positive feedback.[11] **KISS1** expression is barely detectable in prepubertal ovaries and abruptly rises during the gonadotropin surge just before ovulation.[12] Kisspeptin (intracerebral) injections given often to prepubertal females in mouse studies promoted early vaginal opening, premature pubertal commencement, increased body weight, and raised levels of LH and oestrogen.[13] Both Kiss1-/- and Kiss1/ mice have decreased weight and size of ovaries in gene knockout models, which may be the result of the absence of big follicles.[14] Actually, pharmacologic research on the effects of kisspeptin on the control of the **HPO** axis in rats and women have found commonalities in a number of different features of those effects. For instance, the ability of kisspeptin to trigger **LH** production in female rats and humans varies during the ovarian cycle, reaching its peak at the preovulatory stage.[15],[16] It is important to remember that during the cycle, in addition to changes at the hypothalamus level, there is also an increase in GnRH signalling in the pituitary, which appears to be a key factor in the formation of the preovulatory surge in women.[17] Through mediating the stimulation of **COX-2** and prostaglandin **E2** synthesis, the **LH** surge is essential for ovulation. Kiss1 expression in rodents is considerably decreased when **COX-2** is inhibited with NS398 and indomethacin, and rat ovulation efficiency is decreased, suggesting that kiss1 may be a possible **COX-2** downstream target. Prostaglandin **E2** treatment significantly reduces indomethacin's influence on kiss1 expression in female rats.[18] The length of GnRH pulses fluctuates throughout the menstrual cycle, there by controlling the fluctuating release of pituitary gonadotropins.[19] In general, preovulatory **LH** secretions cause a decrease in GnRH release. Elevated oestrogen levels excite Kiss1 neurons in the AVPV, which are responsible for the initial climb of active progesterone levels, during the last phases of the follicular process.[20] This causes **GnRH** pulses to last longer and be stronger, which enhances the **LH** surge and speeds up the ovulation process. Following ovulation, progesterone and **FSH** levels rise, follicular growth improves, and the frequency of GnRH pulses reduces in an autocrine or paracrine manner.[21-22]

2.3 Kisspeptin in Ovulation

The **GnRH** plays a critical role in the reproductive system by stimulating the synthesis of both LH and FSH, with slow GnRH pulsatility (1 pulse every 2 to 3 hours) favouring FSH secretion and fast pulse frequencies (> 1 pulse per hour) promoting LH secretion. Throughout the menstrual cycle, the frequency of **GnRH** pulses fluctuates, control the influence of differential synthesis of pituitary gonadotropins.[23]

Many factors either directly or indirectly influence the **GnRH** secretion. **GnRH** is typically decreased by gonadal steroid feedback, with the exception of the pre-ovulatory **LH** surge. Together with activating progesterone receptors, increased oestrogen levels during the end of the follicular phase also activate **KISS1** neurons in the **AVPV**, boosting **GnRH** pulse frequency and amplitude and causing the **LH** surge and ovulation.[24] Kisspeptins have gained recognition as the most effective **GnRH** and **GPN** secretion activator in primates and rodents over the past 20 years.[25]

2.4 Kisspeptin in oocyte maturation

Kisspeptins mediate the maturation of ovarian follicles by triggering gonadotropins in the hypothalamus and pituitary. Gonadotropins influence granulosa cells and cause the ovary to express Kisspeptin. Kisspeptins can also cause oocyte maturation by binding to kisspeptin receptors in the oocytes.[26] By acting predominantly on

hypothalamic **GnRH** neurons tincrease gonadotropin production, Kisspeptins which are essential for the control of ovulation and fertility and are encoded by the Kiss1 gene.

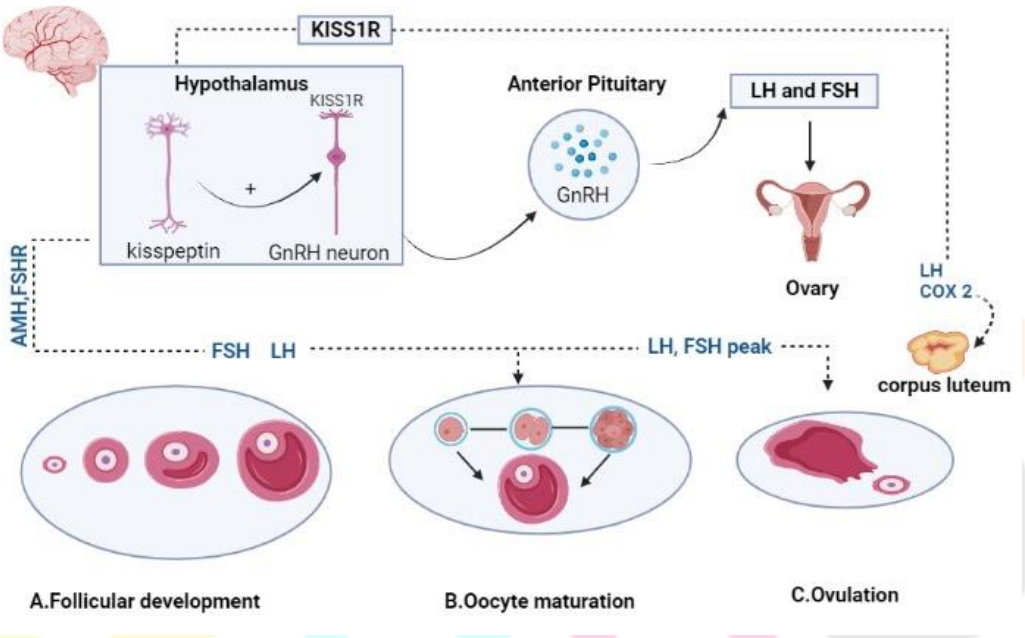
Figure 1: Role of Kisspeptin **in Female reproduction** (Figure created with BioRender.com).

A. Follicular development: primary follicle, secondary follicle, tertiary follicle, large antral follicle.

B. Oocyte maturation: mature follicle.

2.5 Kisspeptin in Pregnancy

Pregnancy is a special physiological state accompanied by a number of morphological, biochemical, and metabolic changes to adequately care for and accommodate the developing foetus.[27] Syncytiotrophoblast cells must be properly implanted and allowed to invade the uterine spiral arteries in order for pregnancy to proceed well and have positive effects on the new born. Kisspeptin plays a crucial role in decidualization and implantation. Kisspeptin interacts with cell adhesion molecules to encourage embryo attachment to the endometrium and encourages stromal decidualization by increasing leukaemia inhibitory factor. [28] Another important way that kisspeptin works during pregnancy is in connection with the maternal immune tolerance that is required to prevent foetal rejection. Indeed, *in vitro* incubation with kisspeptin at levels corresponding to those found in pregnancy, results in increased differentiation of human naive T cells into T-regulatory cells. [29]



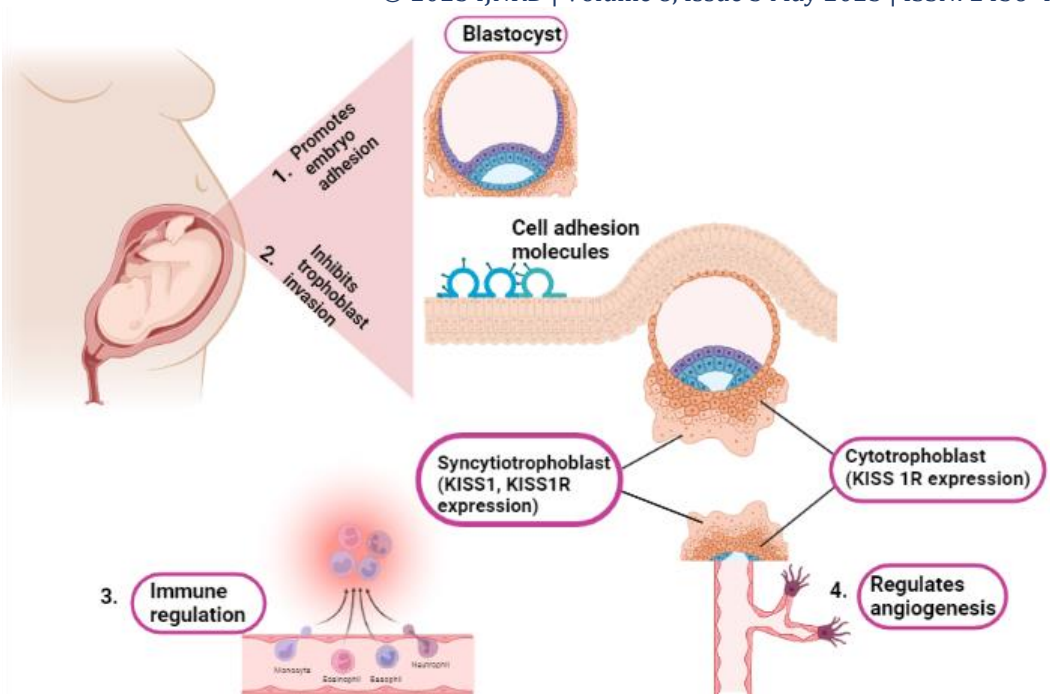


Figure 2: Role of Kisspeptin in Embryo implantation.

Successful implantation requires communication between the blastocyst and a receptive uterine epithelium. Kisspeptin initially promotes embryo attachment to the endometrial epithelium through interaction with cell adhesion molecules. Once the blastocyst penetrates the epithelium, the trophoblast cells differentiate into the inner cytotrophoblast and outer syncytiotrophoblast cells. Whilst the cytotrophoblast cells express the kisspeptin receptor (*KISS-1R*), the syncytiotrophoblast cells express both *KISS-1R* and the kisspeptin gene (*KISS-1*). Kisspeptin subsequently regulates implantation by inhibiting excessive trophoblast invasion into the endometrium. Finally, kisspeptin also has roles in uterine spiral artery remodelling and immune regulation to avoid maternal foetal rejection. (Figure created with Bio.render.com).

2.6 Kisspeptin – An effective physiological trigger for oocyte maturation in in-vitro fertilization treatment

Ovarian hyperstimulation syndrome, a potentially fatal illness, can arise from in vitro fertilisation treatment, which enables infertile couples to conceive. Human chorionic gonadotropin usage in current **IVF** methods to trigger oocyte maturation is the main contributor to **OHSS**. [30] **HCG**, which is pharmacologically used to stimulate oocyte maturation in present **IVF** treatments, is the main contributor to **OHSS**. Due to an unexpected over-response, **OHSS** is one of the main causes of premature **IVF** cancellation before egg retrieval.[31] This harmful side effect could be avoided by creating a more physiological trigger for oocyte maturation, which would increase the safety of **IVF** treatment.[30] **IVF** therapy has utilised kisspeptin, a critical central regulator of reproduction, as a trigger for oocyte maturation.[32] Kisspeptin's primary method of action is to stimulate the release of **GnRH** from the hypothalamus, but it may also have direct ovarian effects that improve oocyte maturation[33-35] and reduce **VEGF** secretion and **OHSS**.[36] In accordance with a recent study update in 2022, Greater physiological concentrations of gonadotropins observed after kisspeptin must be compared to currently available clinical triggers in a direct prospective randomised comparison in order to determine their impact on clinical outcomes. However, Retrospective data indicates that **OHSS** rates have reduced and at least equal live birth rates. Therefore, additional clinical investigation is required to establish the reliability of employing kisspeptin to commence oocyte maturation and to direct future clinical practise.

2.7 Kisspeptin in Lactation

Following IV Kisspeptin 10 injection to female rats, there is a temporary increase in plasma oxytocin levels; however, Kisspeptin 10 intra-cerebroventricular injection had no impact on oxytocin blood levels after administration. On the other hand, the amount of oxytocin released was decreased by the lack of vagal afferent input; overall, these findings supported the hypothesis that Kisspeptin 10 indirectly activates oxytocin neurons while acting on peripheral targets more like a hormone than a neuropeptide. Recent Scientific investigations have shown that oxytocin neurons were activated by central Kisspeptin 10 injection at the end of pregnancy and during lactation, suggesting that oxytocin release by Kisspeptin induction is necessary for parturition and lactation. Although oxytocin release may be quickened by increased plasma Kisspeptin during pregnancy, oxytocin receptor expression and sensitivity were always minimal before childbirth. Yet, research has revealed that administering prolactin to mice have significantly reduced Kisspeptin expression in the hypothalamus, which in turn reduced **GnRH** release. Likewise, utilising bromocriptine as a prolactin suppressor was linked to a considerable upsurge in the expression of Kiss1 mRNA the third ventricle of mice, namely in its rostral periventricular area (RP3V). The estrous cycle was also shut down in rats due to decreased **LH** secretion during lactation and decreased Kiss1 mRNA expression in the hypothalamus. In fact, lactation produces a period of infertility in almost all mammals, ensuring the offspring's healthy growth and survival, and the proper reduction of Kisspeptin expression aids in lactational anovulation. [36]

3. ROLE OF KISSPEPTIN IN MALE REPRODUCTION:

Kisspeptin is a well-known regulator of the onset of puberty, sexual development, and adult reproductive activity. Kisspeptin stimulates gonadotropins (luteinizing hormone, follicle-stimulating hormone, and downstream sex hormones (testosterone and oestradiol) via acting on **KISS1R** on hypothalamic gonadotropin-releasing hormone neurons.[37] The first "kisspeptin into human" study, which was conducted in 2005, demonstrated that kisspeptin can promote the release of reproductive hormones in men.[38] There are numerous reported reproductive diseases that are caused by disruptions to the central **KISS1/KISS1R** pathway. Hypogonadotropic hypogonadism is brought on by **KISS1R** inactivating mutations, whereas precocious puberty is brought on by activating mutations. With their two primary activities, steroidogenesis and spermatogenesis, the testes are crucial for male reproduction. Several studies have noted **KISS1**/distribution, **KISS1R**'s expression, and activity in the testis.[39,40,41] Additional evidence that **KISS1/KISS1R** may have a direct role in testis physiology comes from the fact that re-expression of **KISS1R** in **GnRH** neurons is insufficient to restore normal testicular function[42]. Research on primates [43-45], rodents, amphibians [46-48] and fish [49] have found potential regulatory roles for kisspeptin in the development of germ cells, the regulation of sperm function, and testicular steroidogenesis.

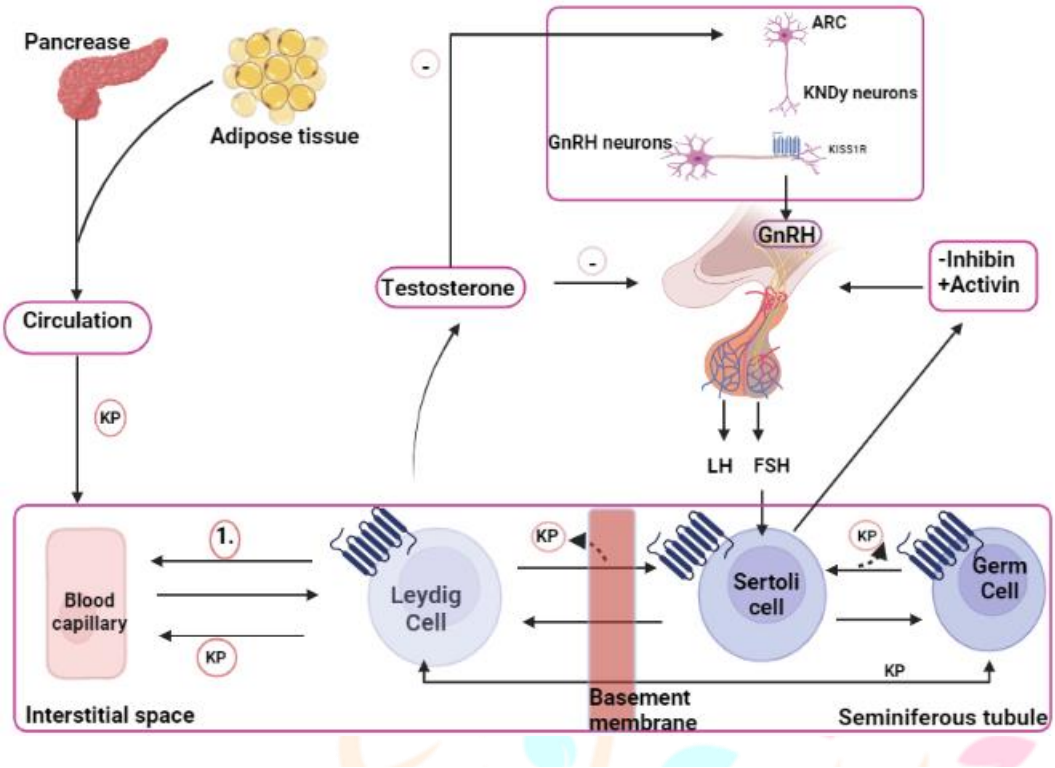


Figure 3 : Potential role of Kisspeptin in Testis.

Kisspeptin and KISS1R are expressed on testicular Leydig, Sertoli and germ cells. This local kisspeptin might have autocrine and paracrine roles. Besides this local kisspeptin, kisspeptin is secreted by hypothalamic KNDy neurons and some peripheral organs — such adipose tissue and the pancreas — that can also reach the gonads via the systemic circulation. The hypothalamic kisspeptin affects testicular activities indirectly via actions on GnRH neurons. GnRH in turn modulates secretion of pituitary LH and FSH. LH and FSH act on Leydig and Sertoli cells, respectively. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; KNDy neurons, kisspeptin, neurokinin B and dynorphin containing neurons; KP, kisspeptin; LH, luteinizing hormone; T, testosterone. (Figure created with BioRender.com).

3.1 Testicular kisspeptin and KISS1R:

Distribution in testicular tissues

One of the major contributing factors to infertility and sperm production is testicular degeneration, which is characterised by deficiencies in sperm viability, motility, and concentration. This obviously affects male fertility.[50] Significant relevance in steroid biosynthesis, spermatogenesis progression, and sperm functions, as well as species-specific changes in localization and potential activities in turns, have been revealed by characterising the kisspeptin system in the testicles of mammals and non-mammalian vertebrates [51,52,53] . Kisspeptin stimulates and promotes the development of spermatogenesis cells in the testis and has a promising future as a pharmacological target for the treatment of issues associated with human spermatogenesis [54]. While kisspeptin signalling in peripheral tissues, particularly in the testicles of mammals and non-mammalian vertebrates, has been well researched, its mandatory function within the testis is still up for debate.[55] Hypogonadotropic hypogonadism is caused by **KISS1/KISS1R** inactivating mutations in humans[56] and mice.[57] **hCG** stimulation tests performed repeatedly over the course of early development, childhood, adolescence, and early adulthood are not able to reverse the dramatic reduction in testosterone production [58]. Hence suggesting a potential direct role for the kisspeptin system in the steroid synthesis which is necessary to maintain the course of spermatogenesis and sperm maturation. In Kiss1R-/- mice's inability to maintain effective

spermatogenesis after conditional Kiss1R reactivation in GnRH-secreting neurons highlights the necessity of intratesticular activity.[59]

3.2 Kisspeptin in spermatogenesis

The initial phase in the differentiation process is the synchronisation of mitotic, meiotic and multi-part process of spermatogenesis, which culminates with the production of male gametes inside the testis. Diploid spermatogonia must first undergo mitosis before being converted into primary spermatocytes by auxocytosis entry in meiosis forming secondary spermatocyte first and then the round spermatids, the haploid cells undergoing spermatogenesis, the differentiation event transforming them into spermatozoa. [55] As a result of hypothalamic GnRH stimulation, peripheral kisspeptin treatment speeds up spermatogenesis. Gain of function mutations in KISS1/KISS1R have consistently been linked to central precocious puberty in humans. On the other hand, In mice and humans, inactivating mutations of KISS1/KISS1R result in hypogonadotropic hypogonadism with a sharp decline in testosterone biosynthesis that is not reversed by brief and prolonged hCG stimulation tests that are repeatedly performed during infancy, childhood, adolescence, and early adulthood, hence suggesting a potential direct role for the kisspeptin system in the steroid synthesis necessary to sustain the development of spermatogenesis and the maturation of sperm . Subcutaneous injection of the artificial Kiss1 pentadecapeptide in non-mammalian species in prepubertal male chub mackerel can hasten spermatogenesis in non-mammalian species.[60] According to gene expression profiling in mammals, the development of spermatozoa and the start of Kiss1/Kiss1r expression in the mouse testis are related[61], demonstrating a relationship between mammalian testicular kisspeptin/Kiss1r system and spermatogenesis. Kisspeptin also inhibits cell chemotaxis and migration, which are critical in the early stages of spermatogenesis and have anti-metastatic effects.[62] Moreover, KP-13 can alter sperm motility and hyperactivate them in the late stages of spermatogenesis, possibly caused by a rise in sperm intracellular Ca2+ concentration. Kisspeptin concentration in seminal plasma and semen quality have a positive association, this demonstrates the significance of the kisspeptin system in the development of sperm. However, it's possible that peripheral kisspeptin is not required for mammalian spermatogenesis. Secondly, on a phytoestrogen diet, reduced levels of spermatogenesis are still seen in Kiss1 and Kiss1r mutant mice. Also, exogenous hormone treatment helps male patients with **KISS1R** mutations acquire fertility. Although testicular kisspeptin as a whole might not be essential for mammalian spermatogenesis, it is a crucial regulator of it. [63]

3.3 Kisspeptin in testicular steroidogenesis

Leydig cells in male testicles secrete androgens, primarily testosterone, which are steroids. The impact of peripheral kisspeptin on Leydig cell androgen synthesis has not yet been determined. First, disruption of Kiss1 expression is linked to lower testosterone levels in rats[63] and the kisspeptin antagonist P234 lowers the production of hCG-activated testosterone in vitro[64] , but local injection of P234 does not change plasma testosterone levels in adult rhesus monkeys.[65,66] Second, despite the fact that the immortalised MA-10 Leydig cell line expresses Kiss1r fails to respond while triggered by KP-10. Moreover, kisspeptin stimulates the production of androgen-binding protein in Sertoli cells, suggesting a possible role for kisspeptin in ABP production. [67]

4 ROLE OF KISSPEPTIN IN PANCREASE AND GLUCOSE METABOLISM:

It was noted that KISS1 was expressed in the human pancreas in addition to the fact that KISS1 was expressed in non-metastatic melanoma cells. These results therefore showed that kisspeptin may play a role in pancreatic development and/or function as early as 1996. [68] Later, the **Kp** gene and its receptor were found to be expressed in beta and alpha cells, respectively, in human and mouse islets. Alpha and beta pancreatic cells colocalized with Kp and its receptor immunoreactivities. [69] Without affecting basal secretion, Kisspeptin-54 (Kp-54) bumped the amount of insulin produced by mouse and human islets in response to glucose. [69] Kisspeptin-10 (**Kp**-10) studies utilising rhesus monkeys [70] and rats [71] confirmed in vitro findings. Additionally, Insulin levels in rats following intracerebroventricular administration of the peptide were unaffected, demonstrating Kisspeptin's peripheral site of action. Results from our group demonstrated that Kiss1 and Kiss1r [mRNA and peptide] are expressed in the pancreas. We have demonstrated that pancreatic Kiss1 mRNA levels were elevated in male diabetic type 1 and type 2 rats. [71] On the contrary hand, Kiss1r was just raised in the DM1 group. Nevertheless, both DM2 and diet-induced obese mice had lower protein levels. Furthermore, neither Kisspeptin concentrations nor its receptors were discovered in the DM1 group (as a result of STZ-induced pancreatic cell injury).Only the diet-induced group's Kiss1r protein levels were decreased.[72] Hence, the Kiss1/Kiss1r system may not work correctly in **DM2/DM1** animals, making it unable to control insulin levels.

5 ROLE OF KISSPEPTIN IN CARDIOVASCULAR SYSTEM:

In xenografted mice tumour model and isolated human placental arteries, kisspeptin prevents angiogenesis [73] Kisspeptin was already known to regulate tumour metastasis and placentation, angiogenesis-related processes, before these research. The Davenport laboratory group addressed the expression of kisspeptin and **KISS1R** in healthy and pathological human vasculature, as well as their potential physiological roles.[74] They discovered that in the healthy and atherosclerotic plaques of the diseased human coronary artery, kisspeptin and KISS1R were both coexpressed in endothelial cells. They also noticed that kisspeptin-1, -13, and -54 caused vasoconstriction in isolated rings of healthy aorta, umbilical vein, and coronary arteries, probably by activating the smooth muscle receptors. Kisspeptin functions as a positive inotrope, enhancing the strength of muscle contractions in the rat, human, and mouse heart; a comparable effect was not observed in Kiss1r null mice. Using strips of rat and human atria, a later examination was carried out in this lab and provided the information presented here.[74] Several studies have shown that the kisspeptin receptor coupling to Gq/11 results in the activation of Rho and Rho-associated kinase, as well as the release of Ca2+ and phospholipase C.[75] If one were to use the Davenport findings, one might initially predict that when kisspeptin levels grow, all pregnancies would become progressively more hypertensive, But since this is not the case, it might be argued that chronically high kisspeptin levels during pregnancy de-sensitize KISS1R, preventing kisspeptin signalling. These intriguing hypotheses highlight the importance of further investigation to identify any potential roles for kisspeptin signalling in cardiovascular physiology in both healthy and sick states.[76,77]

6 ROLE OF KISSPEPTIN IN LIVER:

In 2020 a study on female rats to ascertain the effects of FA profiles in blood, liver, WAT, and total body weight following chronic central kisspeptin and kisspeptin receptor antagonist P234 administration.[78] In 2022, a study

gives concrete evidence that genetic and pharmacological therapies targeting the **KISS1R**-mediated signalling pathway can prevent the onset of **NAFLD**. Also, the research results confirmed the theory that in insulin-resistant obese mice, hepatic KISS1R deficiency increases hepatic steatosis. In the context of hepatic KISS1R impairment, the expression of genes related to lipogenesis is increased. The genes involved in **TG** synthesis and mitochondrial activity are modulated by hepatic **KISS1R** deficiency. Biomarkers for insulin resistance, hepatic inflammation, and hepatic fibrosis are increased by hepatic **KISS1R** deficiency. In a wild-type mouse model of **NAFLD**, **KISS1R** agonist reduces hepatic steatosis and metabolic impairment. In isolated primary mouse hepatocytes, **KISS1R** signalling directly activates **AMPK** via Gq/11 and suppresses **TG** production. The study's findings also demonstrated that the hepatic **KISS1R** signalling pathway inhibits **NAFLD** via **AMPK**, making **KISS1R** an adequate therapeutic target for the treatment of **NAFLD**.[79]

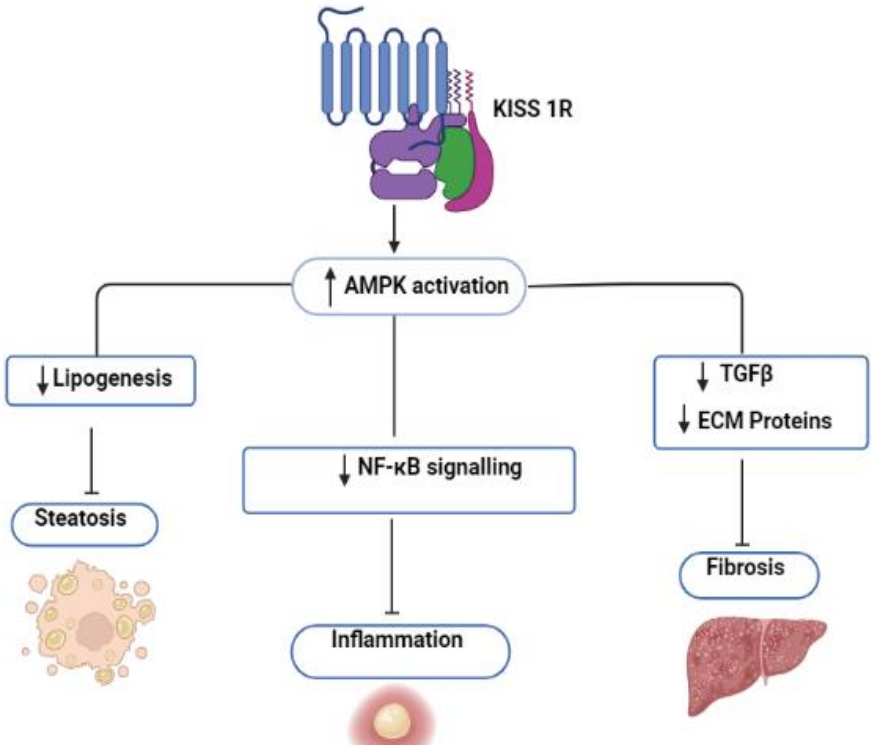


Figure 4: Kisspeptin role in Liver. (Figure created with BioRender.com)

7 ROLE OF KISSPEPTIN IN KIDNEY:

The first concrete proof that kisspeptin is crucial for kidney health has been given in 2010.[80] In accordance with the researchers, Kisspeptin and KISS1 (GPR54) receptors are present in the tubular cells, collecting duct cells, and vessels of smooth muscle cells in rat kidneys. It was reported that chronic renal failure drastically reduced **KISS1R** protein levels. Moreover, absence of the **KISS1** receptor resulted in renal failure due to defects in embryonic branching morphogenesis, impaired glomerular development, and decreased glomerular count in adult kidneys.[81] In 2010, a chronic renal failure rat model to explored changes in the kisspeptin and kisspeptin receptor expression in the kidney of 5/6 nephrectomized rats with and without chronic renal impairment. This research shows altered kisspeptin and kisspeptin receptor expression in chronic renal impairment kidney tissues, implying that these proteins may have a pathophysiological role in chronic renal failure. [80] Last but certainly not least, the remnant kidney of 5/6 nephrectomised rats which represents the rat model of chronic renal failure demonstrated altered expression of Kisspeptins and KP receptor for the first time. These findings have brought

up speculation that KPs and their receptor are involved in the pathogenesis of chronic kidney failure and the local regulation of renal function. A study on the relationship between kidney function, Ang II, ACE, aldosterone, and kisspeptin were studied in connection to renal function in experimental kidney I/R injury in male Sprague-Dawley rats. Following the study, kidney kisspeptin and urine kisspeptin levels were greater in the experimental group with experimental acute renal failure (I/R group). [82]

8 FUTURE PERSPECTIVE:

Over 2 decades Kisspeptin has gained an increasing attention for its benefits towards reproductive system both male and female. Lifestyle changes in individuals created a major negative impact by increased reproductive disorders in both Male (infertility) and Female PCOS, PCOD, infertility, pathogenesis in pregnancy, etc. An article by Maxine Myers from Imperial College London stated, Low sex drive in both men and women may be treated with kisspeptin hormone injection who having HSDD. They also concluded that it was well tolerated with no side effects which is crucial from a drug development point of view. In future years I believe Kisspeptin hormone injections would be a potential therapeutics in Psychosexual Disorders like unexplained Libido.

9 ABBREVIATIONS:

1.**KISS1** - Kisspeptin 1
2.**KISS1R** - Kisspeptin 1 receptor
3.**KP** - Kisspeptin
4.**GnRH** - Gonadotropin Releasing Hormone
5.**IVF** - in-vitro Fertilization
6.**HPG** - Hypothalamic Pituitary Gonadal
7.**HPO** - Hypothalamic Pituitary Ovarian
8.**LH** - Luteinizing Hormone
9.**FSH** - Follicular Stimulating Hormone
10. **GABA** - Gamma-Aminobutyric Acid
11. **AVPV** - Anteroventral Periventricular Nucleus
12. **PcG** - Polycomb
13. **TrXG** - Trithorax
14. **POA** - Preoptic Area
15. **E2** - Estradiol
16. **CoX-2** - Cyclooxygenase-2
17. **GPN** - Gonadotrophin
18. **LIF** - Leukaemia Inhibitory Factor
19. **OHSS** - Ovarian Hyperstimultion Syndrome
20. **hcG** - human chorionic Gonadotropin.
21. **VEGF** - Vascular Endothelial Growth Factor
22. **Icv** - Intracerebroventricular
23. **RP3V** - Rostral Periventricular

24. **SPG** - Spermatogonium
25. **ISPC** - Primary Spermatocytes
26. **IISPC** - Secondary Spermatocytes
27. **SPT** - Spermatids
28. **SPZ** - Spermatozoa
29. **ABP** - Androgen-Binding Protein
30. **DM1** - Diabetes Mellitus1
31. **DM2** - Diabetes Mellitus2
32. **DIO** - Diet-Induced Obesity
33. **STZ** - Streptozotocin
34. **FA** - Fatty Acid
35. **WAT** - White Adipose Tissue
36. **NAFLD** - Non-Alcoholic Fatty Liver Disease
37. **TG** - Triglyceride
38. **AMPK** - AMP-activated protein kinase
39. **Ang II** - Angiotensin II
40. **ACE** - Angiotensin Converting Enzyme
41. **I/R injury** - Ischemia Reperfusion injury
42. **PCOS** - Polycystic Ovarian Syndrome
43. **PCOD** - Polycystic Ovarian Disorder
44. **HSDD** - Female Hypoactive Sexual Desire Disorder

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