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Physiogical Role of Kisspeptin in The Hypothalamic-Pituitary-Gonadal Axis

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SUMMARY

In neurohormonal system, mammalian reproductive axis is regulated by combination of three fundamental tissues and parts; these are hypothalamus, hypophysis and gonads. Females, the main physiological function of the hypothalamic-pituitary-gonadal axis (HPG) in the reproductive performance of activities required for continued secretion of hormones, ovum acquisition, to ensure continuation of pregnancy with the formation of a healthy pregnancy. This is part of a triple hypothalamic gonadotropin axis releasing hormone (GnRH), pituitary follicle-stimulating hormone (FSH) and luteinizing hormones (LH), estrogen and progesterone in the ovary is the part. Classical information is released from the hypothalamus, GnRH, pituitary receptors in the hypothalamic-pituitary portal circulation through the front of the high-density gonodrop cells and stimulates FSH and LH are secreted from these cells. Follicle-stimulating hormone, stimutales the release of ovarian follicle development and estrogen hormone, ovulation takes place in the LH. The hypothalamus, pituitary and gonadal axis GnRH-FSH/LH-estrogen/progesterone way to the front of many mammalian species, although well-defined molecular and cellular events that started in the brain function is not fully understood yet. But in recent years the discovery of *kisspeptin*, particularly in GnRH secretion, puberta and metabolic regulation of reproduction has resulted in many of the unknown. The Kiss1 gene encodes a family of peptides called kisspeptins, which are the natural ligands for the receptor *G protein-coupled receptor* (GPR54). In humans and mice, inactivating mutations of GPR54 results in hypogonadotropic hypogonadism, indicating that kisspeptins play a vital role in the regulation of GnRH secretion. Many aspects of the roles of kisspeptins on the neuroendocrine regulation of reproduction are still not clear, despite the knowledge of their regulatory effects on timing puberty and hypothalamic-pituitary-gonadal axis. The aim of this review, to contribute our knowledge about structure of the kisspeptins, neuronal control and draw attention the importance role kisspeptins of in reproductive and nervous system and shed light on future studies.

Key Words: *Kisspeptin, GPR54, GnRH, FSH, LH, Puberty*

ÖZET

Hipotalamo–Hipofizer-Gonadal Aks'ta Kisspeptin'in Fizyolojik Rolü

Nörohormonal sistemde, memeli üreme aksı üç temel doku ve bölümün birleşmesiyle düzenlenir; bunlar hipotalamus, hipofiz ve gonadlardır. Dişilerde, hipotalamo-hipofizer-gonadal (HPG) aksın temel fizyolojik fonksiyonu reproduktif faaliyetlerin devamı ve performans için gerekli hormonların salgılanmasını, ovumun elde edilmesini, gebeliğin oluşumunu ve sağlıklı gebeliğin devamını sağlamaktır. Bu üçlü aksın hipotalamus kısmını gonadotropin serbestleyici hormon (GnRH), hipofiz kısmını follikül uyarıcı (FSH) ve lüteinleştirici (LH) hormonlar, ovaryum kısmını ise östrojen ve progesteron oluşturmaktadır. Klasik bilgi olarak hipotalamustan GnRH salınmakta, hipotalamo-hipofizer portal dolaşımla yüksek yoğunlukta ön hipofizdeki reseptörler aracılığı ile gonodrop hücreleri uyarmakta ve bu hücrelerden FSH ve LH salgılanmaktadır. Folikül uyarıcı hormon, ovaryumda follikül gelişimini ve östrojen hormonunun salınımını uyarırken, LH ise ovulasyonu gerçekleşmektedir. Hipotalamus, hipofiz ve gonadal aks da GnRH-FSH/LH-östrojen/progesteron yolu bir çok memeli türünde iyi tanımlanmış olmasına rağmen ön beyindeki bu işlevi başlatan moleküler ve hücresel olaylar henüz tam olarak bilinmemektedir. Fakat son yıllarda *kisspeptinin* keşfedilmesi, başta GnRH salınım olmak üzere, puberta ve üremenin metabolik düzenlenmesinde birçok bilinmeyenin ortaya çıkmasına neden olmuştur. Kisspeptinler, peptit bir aileden oluşan ve *Kiss 1* gen tarafından kodlanarak *G protein-coupled receptor* (GPR54)'e bağlanan hormonlardır. İnsanlarda ve farelerde GPR54 mutasyonlarındaki eksiklik ya da yetersizlikler hipogonadotropik hipogonadizmle sonuçlanmıştır. Bu da kisspeptinlerin GnRH sekresyonu düzenlemesinde hayati bir rol üstlendiğini göstermektedir. Kisspeptinlerin pubertenin zamanlanması ve HPG aks regülasyonunda etkili oldukları bilinmekle birlikte üremenin nöronal kontrolü açısından açıklığa kavuşturulmayı bekleyen pek çok nokta bulunmaktadır. Bu derlemenin amacı, kisspeptinlerin yapısı, nöronal kontrolü hakkındaki bilgilere katkı sağlayarak, üreme ve sinir sistemindeki rolleri açısından kisspeptinlerin önemine dikkati çekmek ve ileride yapılması planlanabilecek çalışmalara ışık tutmaktır.

Anahtar Kelimeler: *Kisspeptin, GPR54, GnRH, FSH, LH, Puberta*

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INTRODUCTION

Reproductive success can be achieved by excellent managed interaction between regulatory signals from brain, hypophysis and gonads. Release of pituitary gonadotrophins, FSH and LH is essential for ovulation and spermatogenesis and those hormones are controlled by feedback effect of gonadal steroids on brain and hypophysis. Strong LH and FSH release is necessary particularly for steroidogenesis and gametogenesis. That release is controlled by negative feedback effect of gonadal steroids sourced from testicles and ovaries and in females, pre-ovulatory LH surge is induced by positive feedback effect of ovarian steroids. Effective factor in brain-hypophyseal-gonadal axis is GnRH which is a decapeptide discovered 30 years ago. Although it was known that gonadal steroids and other peripheral signals have a collective negative and positive feedback effect on GnRH secretion of brain, the cellular and molecular mechanism was not clear. A major revolution has occurred after understanding neural control of reproductive signals in 2003. In accordance with results it was discovered that deletions and mutations of gene GPR54 result in hypogonadotrophic hypogonadism and sexual infantilism in human and rat. Discovery of this relation between GPR54 and reproduction was draw attention on receptor GPR54 which also known as receptor of messenger molecule kisspeptin (Jeremy 2008).

Many aspects of the roles of kisspeptins on the neuroendocrine regulation of reproduction are still not clear, despite the knowledge of their regulatory effects on timing puberty and hypothalamic-pituitary-gonadal axis. This review examines the physiological role of kisspeptin and the kisspeptin receptor in the control of gonadotrophin and gonadal steroid hormone secretion. In addition, in the review attempted to present; structure of kisspeptins and ranging from the anatomical distribution kisspeptins neurons of mammal species, different mechanisms and influence between the species on the reproductive system and HPG axis.

1. Kisspeptins and Kisspeptin Receptor (GPR54)

It was first expressed in studies about melanoma and breast cancer in 1995 and 1996 that GPR54 and its ligant (Kisspeptin) are product of metastasis suppressing gene in breast cancer and melanomas. Thus, it was initially named as "metastine" and re-named as kisspeptin in subsequent years. Affix "ss" in word Kiss expresses supressor sequence while prefix Ki refers to the famous chocolate *Kiss* of Pennsylvania, the place where the molecule was discovered in. Hence the gene in charge of Kisspeptin synthesis is named Kiss-1 (Lee and Welch 1997).

1.1. Kiss-1 Neurons and Genomic Structure of Kisspeptins

Kiss1 mRNA transcripts first identified in human brain then followed by anteroventral periventricular nucleus (AVPV), periventricular nucleus (PEN), anterodorsal preoptic nucleus (ADP), medial amygdala and arcuate nucleus (ARC) in rat. Similarly, it was identified in ARC and POA (preoptic area) in sheep (Smith et al. 2006).

Kisspeptins belong to a neuropeptide family which are coded by Kiss-1 gene (lq32). The product of this gene, prepro-kisspeptin, is Kiss-1 protein consists of 145 aminoacids. First part with 19 amino acids is the signal sequence. Protein includes cut-points per 57th and 67th positions. New protein formed by sequestration of amino acids between 121st-124th positions and its C-terminal is amidated. This section is responsible for binding to GPR54 and necessary for intracellular Ca^{+2} stimulation. Phospholipase-C activates and intracellular intensity of inositol (1,4,5) triphosphate and Ca^{+2} is increased, ERK (extracellular signal regulated kinases) and mitogen activated protein kinase pathway p38 is activated following binding of kisspeptin to GPR54 (Aparicio 2005; Durmaz and Dikmen 2007).

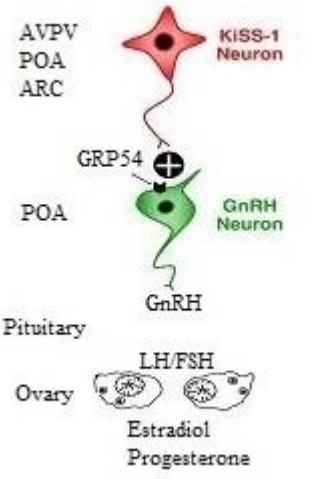

Figure 1. Kiss1 neurons (Smith et al. 2006).

Neuropeptides which include arginine-phenylalanine (Arg-Phe) in C-terminal are classified as RF-Amides. All of the RF-Amides identified until today were shown to be active directly or indirectly on reproductive-neuroendocrine axis (Durmaz and Dikmen 2007).

Kisspeptins and gonadotropin inhibitory hormone are (GnIH) RF-Amides. Gonadotropin inhibitory hormone was first identified in birds. Gonadotropin inhibitory hormone inhibits gonadotropin release both *in vivo* and *in vitro* conditions (Durmaz and Dikmen 2007).

Major form of Kisspeptin in circulation and tissues is metastine which consists of 54 amino acid residues. Besides, shorter forms which include 10, 13 and 14 amino acids (kisspeptin-10, kisspeptin-13 and kisspeptin-14) are naturally available. C-terminal of all kisspeptin forms include Arg-Phe-NH_2 structure similar to metastin (Kotani et al. 2001; Castellano et al. 2006).

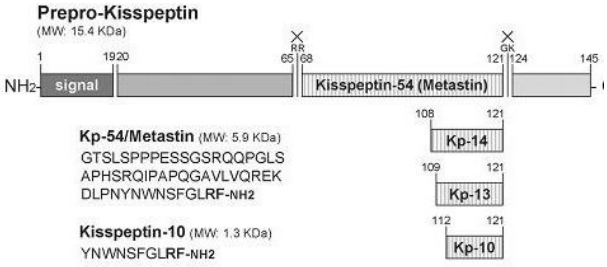

Figure 2. Structure of Kisspeptins (Durmaz and Dikmen 2007).

Kisspeptin receptors were named as GPR54 in rat, AXOR12 in human and Kiss-1R in all creatures. GPR54 is a receptor consists of 396 amino acids. It is also a member of rhodopsin family. It was discovered that human GPR54 is 85% homologous with rat, 80% with mouse and 40% with non-mammalian species (Navarro et al. 2004).

1.2. Activational Effects of Kisspeptins on GnRH

In 2004, Gottsch et al. showed that mRNAs of Kiss-1 were expressed in certain regions of brain which control GnRH release in mouse. Those regions are arcuate nucleus (ARC),

periventricular nucleus (PeN) and anteroventral periventricular nucleus (AVPV) (Gottsch et al. 2006).

Signals formed by binding of kisspeptins to GPR54s in hypothalamic GnRH neurons provide GnRH release from median eminence to hypophyseal circulation. Gonadotropin releasing hormone binds to its receptors in hypophysis and provide release of gonadotropines (FSH, LH) from the gland (Terasawa and Fernandez 2001; Grumbach 2002; De Tassigny and Colledge 2010).

It is assumed that GPR54 in GnRH neurons is the only receptor of kisspeptin and its primary function is to support GnRH secretion. It was shown in various animal experiments that transcription of Kiss-1 and GPR54 genes in hypothalamus is increased during puberty (Terasawa and Fernandez 2001; Grumbach 2002; Aparicio 2005). In a study found that kisspeptin implementation is applying an earlier date the age of the vaginal opening and cycles seeing age up, increases serum levels of GnRH and LH on the 33rd day prepubertal rats (Taskiran 2014).

It is not known that how the kisspeptins stimulates GnRH release by intracellular signal mechanisms. But, as expressed above, it is known that GPR54 signal is formed via Gq-linked G protein thus intracellular calcium concentration, IP (inositol triphosphate) cycle and ERK activation via MAP kinase are increased. However, it is not known clearly that how all those mechanisms induce GnRH secretion (Colledge 2004; Durmaz and Dikmen 2007).

1.3. Hormonal Regulation of Kiss-1 and GPR54

Navarro et al. (2004) reported that sex steroids estrogen (E) and testosterone (T) inhibits mRNA expression of Kiss-1 in hypothalamic arcuate nucleus. According to hypothesis of those researchers, increased E nad T levels in circulation inhibits expression and secretion of kisspeptins in arcuate nucleus thus decrease GnRH release from GnRH neurons. As E and T levels in circulation decreases the inhibiton stops, kisspeptin synthesis in ARC is stimulated and GnRH release is increased. The study of Smith et al. (2006) disproves this hypothesis. Those researchers showed that sex steroids induce expression of Kiss-1 mRNA in some regions of brain while they inhibit it in some other regions. It was shown in male mice that testosterone inhibits Kiss-1 expression in ARC while it stimulates the same in AVPV. It is thought that steroid-dependent inhibition in arcuate nucleus is accompanied with both androgen receptor (AR) and estrogen receptor-α (ER_α) together. ARs in arcuate nucleus show 65% colocalisation with mRNAs of Kiss-1 while the colocalistion of ER_α is 88% with the same. However, ER_α is thought to accompany T dependent Kiss-1 mRNA induction in AVPV following aromatisation of testosterone. Opposite effects of T on Kiss-1 mRNA expression in those two regions can be explained by different expressions of AR and ER in those two nucleuses (Navarro 2004; Smith et al. 2006; Skorupskaite et al. 2014).

In female mice, E inhibits Kiss-1 mRNA expression in ARC while it induces the same in AVPV. Almost all of the Kiss-1 cells have ER_α in females but a portion of 25-30% have ER_β (Navarro 2004). The research shows that E dependent regulation was lost in ER_αKO mice while it was intact in ER_βKO mice prooving that E dependent regulation is achieved via ER_α. The molecular mechanism of different effects of estrogen on Kiss-1 expression in ARC and AVPV is not known yet. But progesteron receptor (PR) is thought to participate in that phenomonia. The researchers observed in their studies that Kiss-1 neurons are localised or too close with PR neurons. Besides the same researchers express that those different effects in E regulation may be due to dopamine. mRNAs of tyrosine hydroxylase and Kiss-1 are colocalised in AVPV while they are not in ARC. Thus it may be thought that dopamine may have role in E dependent Kiss-1 expression in AVPV (Smith et al. 2006; Toporikova et al. 2014; Dubois et al. 2014).

Different regulation of Kiss-1 mRNA in prosencephalic nucleuses is important for Kiss-1 to show different physiological functions in HPG axis. Arcuate nucleus is the negative feedback center for GnRH and gonadotropin secretion while AVPV is the regulation center for positive feedback responsible of LH surge in females (Aparicio 2005; Whitlock et al. 2010).

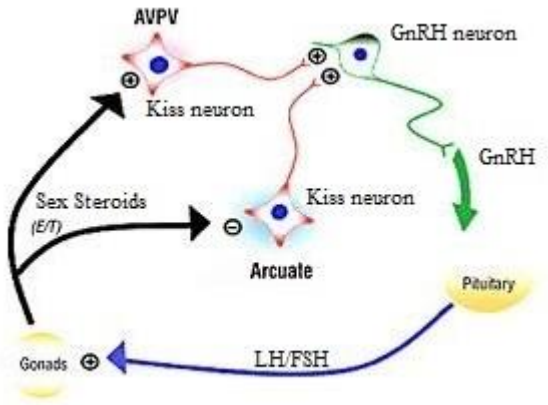

Figure 3. Kisspeptin stimulates GnRH secretion (Whitlock et al. 2010).

Expression of Kiss-1 mRNA in anteroventral periventricular nucleus of female is higher than that of male. Moreover it is thought that neurons in AVPV have synapses with GnRH neurons. There are plenty of $ER_{\alpha,\beta}$ and PR in anteroventral periventricular nucleus. Those cause LH surge by increasing its secretion as binded by their ligands. E dependent Kiss-1 mRNA induction in female may have role in GnRH/LH surge during preovulation (Funes et al. 2003). Hence, showing that kisspeptin neurons in AVPV differs by gender. Those neurons thought to have role in formation of GnRH/LH surge in female and regulation of sexual behaviours in male. Unlike anteroventral periventricular nucleus, Kiss-1 mRNA level in ARC is the same between female and male. Thus indicating that the role of kisspeptin neurons in arcuate nucleus of female and male are the same. It is expressed that kisspeptins have role in negative feedback inhibition of gonagotropin secretion by gonadal steroids in that region (Tena-Sempere 2006; Kuohung and Kaiser 2006).

1.4. GPR54 Gene Mutations

Gene GPR54 which is heptahelical, G protein-linked and consists of 398 amino acids codes a receptor which has homology with galanin and opioid family (Funes et al. 2003; Aparicio 2005).

It was reported that mutations in GPR54 gene causes idiopathic hypogonadotrophic hypogonadism (IHH) in human and mouse. It was shown that FSH and LH release from hypophysis is realised by exogenous GnRH administration in IHH cases with no gonadotropin secretion in human and mouse. It was reported that the GnRH concentrations of the hypothalamus extracts of GPR54 knock-out (GPR54KO) mice and control group were the same. Those results verify that GPR54 has role in GnRH release (Lee et al. 1996; Liu and Herbison 2015).

In a study performed on 1 sister and 4 brothers with

idiopathic hypogonadotrophic hypogonadism history it was reported that gene GRP54 is localised on 19p13 region and a deletion of 155 bp identified in 3 end of intron 4 and 5 end of exon 5 and consequently receptor function was lost (Lee et al. 1996).

Two different mutations of gene GPR54 were determined in a black male patient with idiopathic hypogonadotrophic hypogonadism diagnosis. One of those mutations was C→T transition, converting the codon at position 331 coding arginine into stop codone (nonsense mutation, R331X) and the other was T→A transversion, converting the stop codone at nucleotide 1195 into arginine codon (nonstop mutation, X399R) (Kuohung and Kaiser 2006).

1.5. Kisspeptin Secretion During Pregnancy

In human, the biggest peripheral source of kisspeptin is placenta. Kiss-1 is localised in syncytiotrophoblast cells in human placenta. And its receptor GPR54 is localised in syncytio, villus and extrovillus trophoblast cells (Terao et al. 2004).

Kisspeptin concentration is low in male and non-pregnant female, however the level of Kiss-1 mRNA and its protein is increased by pregnancy. The mean kisspeptin concentration in male and non-pregnant female is 1,3 pmol/L. The mean kisspeptin level in maternal plasma in first trimester of pregnancy was 1230 pmal/L while it was 4590 pmol/L in second and 9590 pmol/L in third trimester. It was reported that plasma kisspeptin concentration is dropped to normal level (7,6 pmol/L) on 5th day after parturition (Terao et al. 2004).

Placental kisspeptins are responsible for continuous release of gonadotropins despite of high levels of sex steroids. Depending on their recent studies, another group of researchers think that high levels of kisspeptin during pregnancy desensitising GPR54 and suppresses hypothalamic-pituitary-gonadal (HPG) axis. Besides it is also thought that placental kisspeptine-10 decreases collagenase activity and migration of trophoblast cells in first trimester (Terao et al. 2004; Sarvestani et al. 2014).

1.6. Kisspeptin in Animals with Seasonal Estrus

Environmental factors such as photoperiod regulates GnRH production and also has regulatory role in HPG. Kisspeptin is thought to intermediate this regulatory role of gonadotropin releasing hormone neurons. Those effects were tried to be exposed in studies performed on Siberia, Syria hamster and sheep. It was reported that Kiss-1 level was decreased in ARC and increased in AVPV and there were optimal conditions for pregnancy in Siberia hamsters having sexual activity during long daylight period. However, Kiss-1 level is increased in ARC and decreased in AVPV during anoestrus in short days. There were no change in AVPV of Syria hamsters while Kiss-1 level in ARC is increased. (Kriegsfeld 2007; Greives et al. 2007; Clarke et al. 2009).

It was reported that kisspeptin level is high during diestrus period when estrogen level is low and it is low during proestrus period when estrogen level is high. During short daylight period with high durations of melatonin release and with increased sexual activity in sheep, also Kiss-1 mRNA in ARC is increased. On the contrary, Kiss-1 expiration in ARC is decreased during long daylight period. It was shown that in sheep in anestrus, continuous kisspeptin infusion for 48 hours was induced preovulatory LH surge and consequently 75% of the animals were ovulated. Inducing effect of kisspeptin on LH surge in acyclic sheep is activated by positive feedback effect of estradiol on gonadotropin secretion. Central administration of kisspeptin in sheep causes dramatic increase of GnRH in cerebrospinal fluid. Continuous intravenous infusion of kisspeptin in sheep throughout breeding season induces FSH and LH increase. Its peripheral administration in sheep increased serum LH concentration but could not increase GH (Seminara 2005; Lents et al. 2008; Sebert et al. 2010).

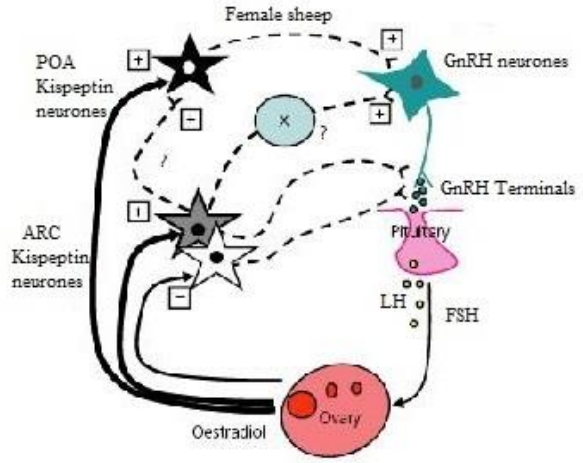

Figure 4. Feedback mechanism in sheep (Seminara 2005).

Kisspeptin neurons are in interaction with GnRH neurons (fiber-fiber interaction) in mare brain. There were kisspeptin entrances in 32% of GnRH immunoreactive cells. Temporal changes of expression of kisspeptin and GnRH during estrus cycle is reciprocal. Kisspeptin administration in mare in estrus brings LH and FSH response but remained insufficient in inducing ovulation. Kisspeptin administration in diestrus mares caused increase in FSH and LH levels (Magee et al. 2008; Magee et al. 2009; Scott et al. 2010).

1.7. Kisspeptin in Animals without Seasonal Estrus

Intravenous kisspeptin administration was increased LH level in cows. Higher LH response in observed after GnRH administration following initial LH increase. Intravenous injection or infusion of kisspeptin is increased LH in cows while it was decreased the stimulatory effect of GnRH on GH secretion (Seminara 2005).

In conclusion, anti-metastatic characteristic of Kisspeptins and related studies in that field will lead our way in understanding metastase causing molecular signals and designating strategy of therapy. Besides, researching the role of Kiss-1 and GPR54 on reproductive neuroendocrinology will answer unexplained questions such as ''what does start puberty?'', ''How estrogen stimulation does form GnRH/LH surge?'', ''How is the mechanism of sexual difference in GnRH surging?''. But more research is needed in this area.

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