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Chapter

Kisspeptin: Role in Female Infertility

Abdulsamed Kükürt, Mushap Kuru, Ömer Faruk Başer and Mahmut Karapehlivan

Abstract

Kisspeptin is a neuropeptide encoded by the kisspeptin gene (Kiss1) and located in different brain regions, primarily in the hypothalamus. Kisspeptin and its receptor G-protein-coupled receptor-54 (GPR54), are also found in behavioural brain regions such as the hippocampus and cortex. Kisspeptin, a very powerful neuropeptide that stimulates the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, does this by increasing gonadotropin-releasing hormone (GnRH) levels. In recent studies, it has been noted that kisspeptin is effective on reproductive functions. Globally 8 to 12% of couples have infertility problems, and the majority are residents of developing countries. Approximately 70% of infertility cases are caused by fertility problems in women. The frequency of infertility in women continues to increase every year and the underlying factors require further research. Bearing this problem in mind, this review examines the possible role of kisspeptin in female infertility. In doing so, it aims to find out how future application of kisspeptin may potentially unravel the neural reproductive disorder.

Keywords: kisspeptin, metastin, GPR54, Kiss1, Kiss1r, infertility, nitric oxide, sex streoid, progesterone, GnRH, LH, FSH

1. Introduction

Infertility is the inability to get pregnant despite regular sexual intercourse for one year or more (without contraception or the impairment of a person's or a couple's fertility) [1]. Fertility and pregnancy rates decrease due to ageing in women. For this reason, it is recommended that women aged 35 and above start receiving infertility treatment after 6 months of conception attempt. After the age of 40, this period should not be waited for treatment. Many factors cause female infertility. These can be listed as medical history (family history, previous treatments, menstrual history, sexual history, etc.), physical factors (weight, body mass index, etc.), diminished ovarian reserves, ovulatory dysfunction (hypothalamic–pituitary axis (HPG axis) disorders, ovarian disorders, thyroid disorders and hyperprolactinemia, etc.), tubal factors, uterine factors and unexplained causes [2, 3]. More than 186 million people worldwide suffer from infertility, and the majority of them are residents of developing countries [4].

Kisspeptin was discovered in 1996 as the product of the kisspeptin gene (Kiss1), which is a metastatic tumour suppressor gene; therefore, it was initially called

metastin [5]. Kisspeptins are a family of neuropeptides in RF-Amide structure [(neuropeptides containing arginine-phenylalanine (Arg-Phe) at the C-terminal are defined as RF-Amides)] [6]. Two years later, the connection between kisspeptin-54 and G-protein-coupled receptor-54 (GPR54) was shown for the first time [7]. In 2003, inactivating mutations of GPR54 were found in people with hypogonadotropic hypogonadism [8]. The respective receptor was previously called the GPR54, it is also identified as the kisspeptin receptor (Kiss1r) nowadays [9].

The detection of the role of the kisspeptin receptor mutation in leading to idiopathic hypogonadotropic hypogonadism paved the way for further investigations about the roles played by the kisspeptin, Kiss1, and Kiss1r systems in the field of reproductive endocrinology [10]. Many studies have shown that kisspeptin plays key roles in the regulation of different aspects of reproduction [11–17]. This review examines the possible role of kisspeptin in female infertility. In doing so, it aims to find out how future application of kisspeptin may potentially unravel the neural fertility disorder.

2. Kisspeptin

The Kiss1 gene encodes the neuropeptide kisspeptins. They, originally identified as metastasis suppressors, were later found to play a central regulatory role in reproduction [18]. The gene is located on human chromosome 1q32. This gene contains 2 non-expressed and 2 partially expressed regions and four exons, assembling the leader peptide consisting of 145 amino acids [19]. This precursor protein transforms into various active forms of kisspeptin with lengths of 54, 14, 13, and 10 amino acids through various post-translational modifications (**Figure 1**) [20]. These forms belong to the RF-amide peptide hormone family, which is closely associated with energy metabolism and reproduction. The members of the RF-amide peptide hormone family contain the common Arg-Phe-NH_2 moiety at the C-terminal [21].

Kisspeptin receptors were first discovered in 2001 in studies about cancer, and they were named as the GPR54. Today, they are identified as the Kiss1r [9]. Kiss1r is a 396-amino acid receptor and a member of G protein-coupled receptors. The minimum length required to activate GPR54 is a 10-amino acid carboxyl terminal sequence (Kisspeptin-10) [22].

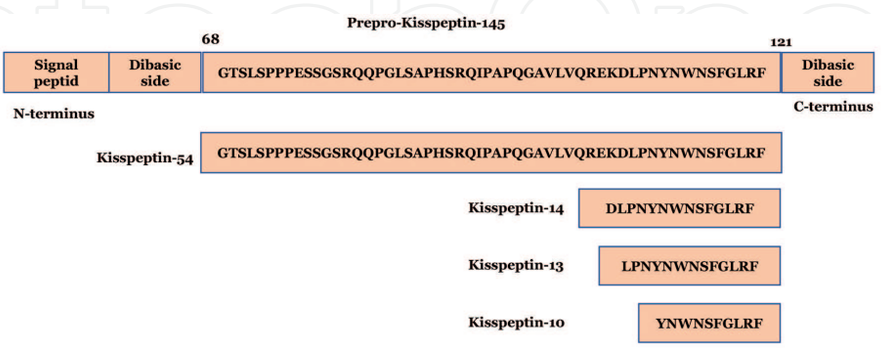

Figure 1.
Amino acids sequence of human kisspeptin isoforms [23, 24].

3. Kisspeptin's mechanism of action

As a result of the kisspeptin binding to the GPR54/Kiss1r receptor, activates the G-protein (G_q/11) and phospholipase-C (PLC). Subsequently, diacylglycerol and

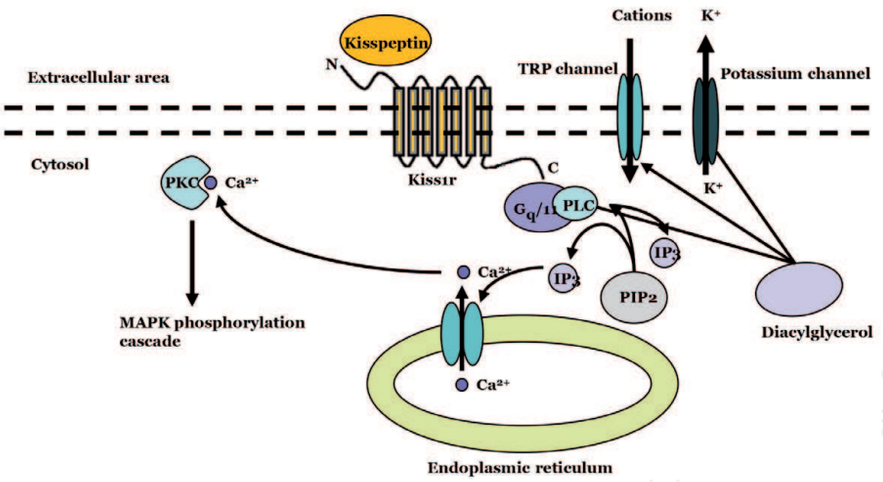

Figure 2.
Cellular action mechanism of kisspeptins [27].

inositol trisphosphate (IP3) are formed from phosphatidylinositol bisphosphate (PİP2), resulting in elevated Ca^{+2} concentrations. Activation of this mechanism results in the closure of the potassium channels and opening of the cation channels (TRP channels), leading to the depolarization of GnRH neurons. Consequently, GnRH neurons start secreting hormones [25]. Kisspeptin increase apoptosis and decrease cell proliferation and metastasis by stimulating the mitogen-activated protein kinase pathway (MAPK) via protein kinase C (PKC) and the extracellular signal-regulated kinase (ERK) pathway (**Figure 2**) [26].

4. Distribution of kisspeptin neurons and effects on the HPG axis

Kisspeptin gene neurons are involved in several actions including steroid hormone feedback, metabolic signalling, and photoperiodic information regulation. It is suggested that, compatibly with their mediator role in steroid hormone feedback mechanisms, Kiss1 neurons are involved in the expression of estrogen receptors (ERα and ERβ) and progesterone receptors [21].

Kiss1 neurons are located in the periventricular nucleus (PeN), arcuate nucleus (ARC) and anteroventral periventricular nucleus (AVPV) which are located in the preoptic area of the hypothalamus (POA) in the brain and which are the regions that regulate the secretion of the GnRH hormone in mouse [28]. Kisspeptins are secreted by these nuclei. However, AVPV displays sexual dimorphism. Kiss1 mRNA expression is higher in AVPV in females compared to males. This indicates that the role of kisspeptin neurons in AVPV varies by gender [29].

The different patterns of Kiss1 mRNA regulation in the forebrain nuclei are important in the emergence of the different physiological effects of Kiss1 on the HPG axis. ARC acts as the negative feedback regulation centre for the GnRH and gonadotropin secretion, while AVPV acts as the positive feedback regulation centre responsible for the LH surge in females. ERα, ERβ, and progesterone receptors are abundant in AVPV. When these receptors bind to their ligands; they increase LH secretion, resulting in the LH surge. Furthermore, Kiss1 neurons in AVPV synapse with GnRH neurons; Kiss1 mRNA expression in AVPV peaks simultaneously with the GnRH/LH release, and the estrogen-dependent Kiss1 mRNA induction in females is involved in the GnRH/LH surge during preovulation [30]. While gonadal steroids inhibit Kiss1 neurons in ARC (negative feedback), they stimulate Kiss1 neurons in AVPV (positive feedback) [23]. Signals arising from kisspeptin

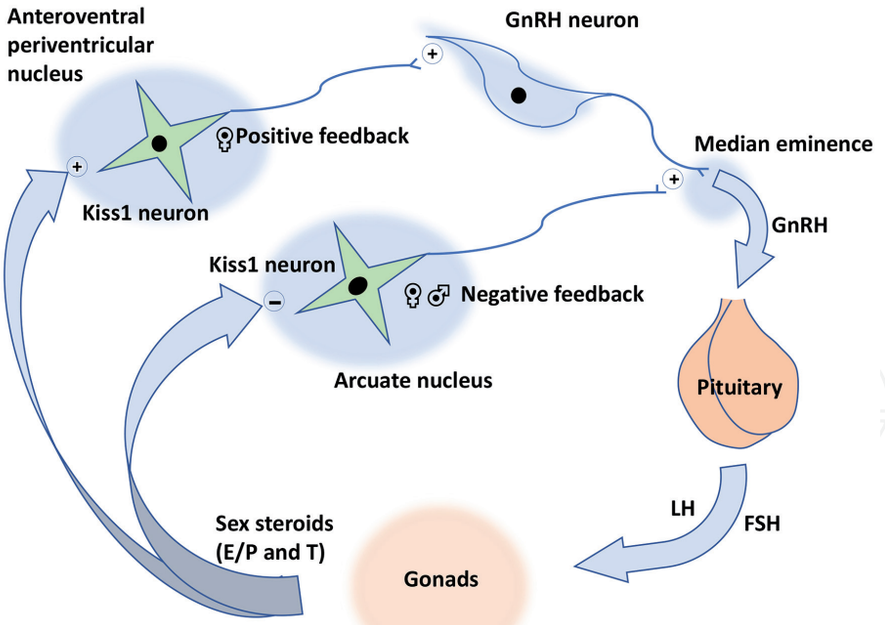

Figure 3.
Kiss1 signalling in mouse brain [32].

binding to GPR54 receptors of the hypothalamic GnRH neurons induce the release of GnRH to the pituitary circulation. GnRH induces the release of gonadotropins (FSH, LH) from the pituitary by binding to the GnRH receptors in the pituitary gland (**Figure 3**) [31, 32].

The molecular mechanisms underlying the different effects of estrogen on the Kiss1 expression in ARC and AVPV is yet to be known. However, progesterone receptors are also thought to be involved in this phenomenon. Kiss1 neurons are colocalized with or stand very close to progesterone neurons in mouse. Tyrosine hydroxylase and Kiss1 mRNAs are colocalized in AVPV but not in ARC. Consequently, it is thought that dopamine is also involved in the induction of estrogen-dependent Kiss1 expression in AVPV [33].

In mouse, ARC Kiss1 neurons synthesize Tachykinin (TAC), neurokinin-B (NKB), and dynorphin (Dyn) in variable quantities depending on species; therefore, they are also known as KNDy (Kisspeptin/Neurokinin/Dynorphin) neurons. NKB and Dyn have been shown to mutually act on kisspeptin neurosecretion [34].

5. The effect of kisspeptin on puberty

The detection of the role of the kisspeptin receptor mutation in leading to idiopathic hypogonadotropic hypogonadism paved the way for studies to further investigate the other roles played by the Kisspeptin, Kiss1, and Kiss1r systems in the field of reproductive endocrinology [10]. The direct/indirect effects of kisspeptin on GnRH neurons leave no doubt that kisspeptin plays a critical role in pubertal activation. Indeed, studies on various species have shown that the Kiss1 and/or Kiss1r expression increases significantly with the onset of puberty [21]. In a study on mice, it was shown that the Kiss1 mRNA expression significantly increased in AVPV during puberty [35]. Also, centrally or peripherally administered kisspeptin in juvenile female rats shortened the timing of vaginal opening by stimulating LH release and ovulation [36, 37]. Similarly, the increase in kisspeptin-54 signal frequency in primates occur at the beginning of puberty, supporting the findings associated with the pubertal increase in kisspeptin secretion [38]. Kiss1 mRNA

expression increases in ARC during puberty along with an associated increase in LH secretion in Rhesus monkeys [39].

Kisspeptin receptor damage impair normal sexual development and to result in the failure of starting puberty. Despite the synthesis of GnRH at normal levels in the hypothalamic GnRH neurons, LH/FSH secretions do not occur and pituitary gonadotropic cells remain unresponsive to externally administered GnRH in such cases [40]. The emergence of problems in the process of starting puberty in the presence of kisspeptin deficiencies has led to the idea that kisspeptin may be an important factor for the start of sexual maturation. This idea has been confirmed by significantly increased levels of released GnRH via kisspeptin injections in mammals and by the acceleration of pubertal start via repeated Kisspeptin injections in juvenile rats. Thus, it has been proven that Kisspeptin certainly participates in pubertal development [41].

A cerebral antibody binds and inactivates kisspeptin in the female rats, impairing or even stopping reproductive functions. Also, the administration of kisspeptin in fasted rats sustains the release of GnRH and that mammals suspend their reproductive functions during states of long-term hunger in order to spend energy only enough to maintain physiological requirements. Nonetheless, the administration of kisspeptin reverses this natural process and restarts reproductive functions [42].

Nitric oxide (NO) is another potential mediator that can affect the onset of puberty since it is a mediator involved in several vital functions such as gonadotropin release, steroidogenesis, folliculogenesis, ovulation, luteal development, luteolysis, and pregnancy [43, 44]. Neuronal nitric oxide synthase (nNOS) is one of the three forms of an enzyme that oxidizes L-arginine to L-citrulline and NO. nNOS neurons in mice and rats contain high densities of ERα [45]. In rats, NO stimulates LH and GnRH release. In mice, deletion of nNOS causes infertility and hypogonadism [46]. Furthermore, recent evidence suggests that kisspeptin may directly act on the release of NO. In adult female mice, kisspeptin close-contacts to nNOS neurons have been observed in the ARC and preoptic region; however, Kiss1r is expressed only from nNOS neurons in the preoptic region [47].

6. Kisspeptin in female infertility

Kisspeptin and neurokinin-B agonists can be used to stimulate the HPG axis in conditions associated with infertility due to central nervous system causes if the system of GnRH neurons is intact. Kisspeptin and neurokinin-B may offer a novel therapeutic approach to treat failures associated with increased/reduced gonadotropin pulsatile secretion. Kisspeptins may be associated with a lower risk of ovarian hyperstimulation syndrome (OHSS) compared to human chorionic gonadotropin (hCG) injections [48]. In polycystic ovary syndrome (PCOS), kisspeptin antagonists can help normalize LH hypersecretion along with ovulation and follicular development [49].

In a study on patients with unexplained infertility (UI), PCOS, and male factor infertility (MFI); In PCOS group kisspeptin levels were measured and found to be significantly higher compared to the MFI and UI groups. The investigators suggested that IU can be treated with kisspeptin injections and that high kisspeptin levels can be a reliable indicator to estimate the antral follicle count (AFC) and to diagnose PCOS [50].

In women with functional hypothalamic amenorrhea (HA) due to low body weight, the administration of kisspeptin-54 acutely stimulates secretion of gonadotropin and that the effect on gonadotropin secretion is significant after the first injection but diminishes considerably (tachyphylaxis) after injections for two

weeks [51]. Nevertheless, the frequency of injections was changed from twice a day to twice a week in another study, and gonadotropin response was sustained [52]. Eight-hour intravenous infusion of kisspeptin-54 has been shown to temporarily increase LH pulse frequency and amplitude in women with hypothalamic amenorrhea [53].

Hyperprolactinemia is one of the leading causes of female infertility as it causes hypogonadotropic anovulation [54]. Since kisspeptin neurons have recently been shown to express prolactin receptors, kisspeptin has been identified as the key mediator involved in this system [55]. In mice, hyperprolactinemia causes anovulation through decreased gonadotropin and GnRH secretion and low levels of kisspeptin expression. Kisspeptin administration in these mice repairs ovarian cycle and gonadotropin secretion. It suggests that kisspeptin neurons have a role in hyperprolactinemic anovulation [56].

Endometriosis is a disease that causes infertility in women [57]. A study conducted in 2012 about endometriosis reported that Kiss1 expression could not be detected in any sample taken from endometriosis patients [58]. In one study, researchers found that the level of Kiss1 expression was statistically significantly higher in endometriosis lesions compared to the level determined in eutopic glandular endometrium and concluded that Kiss1 might have a possible role in the pathogenesis of endometriosis [59]. Another study reported that Kiss1r mRNA levels were statistically significantly higher in the cumulus cells of endometriosis patients compared to healthy oocyte donors. In consequence, researchers argue that the increased Kiss1r expression may be one of the many factors involved in the root cause of endometriosis and related infertility [60].

A study in women suffering from infertility, investigating the genetic association between the neurokinin (TAC3/TAC3R) systems and kisspeptin (Kiss1/Kiss1r) and investigating the expression of these systems, found that the expression of Kiss1, TAC3, and TAC3R was downregulated in the cumulus cells. Similarly, these three genes have been reported to be downregulated in older women with age-related infertility [60]. In that study, these findings could only be attributed to age because infertile patients were significantly older than healthy donors and because the endometriosis patients were younger and showed just an opposite expression profile compared to all other patients, including patients with age-related infertility and low responders [61].

7. Conclusion

This review has examined the association of kisspeptin with female infertility and concluded that kisspeptin has a key role in the HPG axis and can be potentially used for the treatment of reproductive disorders including hypogonadism, ovarian hyperstimulation syndrome (OHSS), polycystic ovary syndrome (PCOS), unexplained infertility (UI), male factor infertility (MFI), hypothalamic amenorrhea (HA), and endometriosis. The literature review revealed that no adverse effects were reported after kisspeptin administration in healthy individuals and patients. Therefore, kisspeptin can be used safely in both healthy and infertile individuals. Especially its positive effects on GnRH and its key role in the initiation of physiological events in the hypothalamic–pituitary-gonadal axis (HPG axis) show that kisspeptin has a say in fertility. For this reason, kisspeptin is an option that should be focused on in the solution of infertility cases that develop in mammals (humans and especially livestock) and are one of the diseases of the age.

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