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Kisspeptins and their synthetic analogues: structure, mechanism of action and prospects for clinical use

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ABSTRACT. The literature review compares native kisspeptin (KP) and its synthetic analogues, including modifications that improve its stability in the human body, and characterizes the possibility of their therapeutic use in the correction of reproductive disorders. KP is a key neuropeptide that regulates reproductive function through activation of the *KISS1*R receptor and stimulation of gonadotropin-releasing hormone (GnRH) secretion. It was found that kisspeptin-10 and kisspeptin-54 have different pharmacokinetics, but KP-10 activates the *KISS1*R receptor no less effectively. The mechanism of action of CP is associated with the activation of the Gq/11 protein cascade, leading to an increase in intracellular calcium and activation of phospholipase C. Modifications of kisspeptins that improve their stability are described, including the replacement of amino acids, the addition of protective groups that slow down degradation and can significantly increase the half-life of the peptide in the blood. The main areas of application of kisspeptins in clinical practice, including in the treatment of reproductive disorders and oncology, are considered. Synthetic analogues of kisspeptin, especially those modified to improve stability, are of significant interest for the development of new therapeutic strategies in the field of reproductive medicine. Synthetic analogs of KP that are resistant to degradation by matrix metalloproteinases (MMP-2/9) are being developed. Phosphine analogs that inhibit MMP and prolong the half-life are promising.

Keywords: kisspeptins, kisspeptin receptor agonist, synthetic analogues, G-protein coupled receptors, impairment of reproductive function

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Обзор

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Кисспептины и их синтетические аналоги: строение, механизм действия и перспективы клинического применения

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РЕЗЮМЕ. В литературном обзоре проведено сравнение нативного кисспептина (КП) и его синтетических аналогов, в том числе с модификациями, улучающими его стабильность в организме человека, и охарактеризованы возможности их терапевтического применения в коррекции нарушений репродуктивной функции. КП представляет собой ключевой нейропептид, регулирующий репродуктивную функцию через активацию рецептора *KISS1*R и стимуляцию секреции гонадотропин-рилизинг гормона (ГнРГ). Установлено, что кисспептин-10 и кисспептин-54 обладают различной фармакокинетикой, однако КП-10 не менее эффективно активирует рецептор *KISS1*R. Механизм действия КП связан с активацией Gq/11-белкового каскада, приводящей к повышению внутриклеточного кальция и активации фосфолипазы С. Описаны модификации кисспептинов, улучающие их стабильность, в том числе замена аминокислот, добавление защитных групп, которые замедляют деградацию и смогут значительно увеличить период полужизни пептида в крови. Рассмотрены основные области применения кисспептинов в клинической практике, в том числе в лечении нарушений репродуктивной функции: при гипогонадотропном гипогонадизме, бесплодии, задержке полового созревания, гормонозависимых опухолях и онкологии. Синтетические аналоги кисспептина, особенно те, что модифицированы для улучшения стабильности, представляют значительный интерес для разработки новых терапевтических стратегий в области репродуктивной медицины. Разрабатываются синтетические аналоги КП, устойчивые к деградации матриксными металлопротеиназами (MMP-2/9). Перспективны фосфиновые аналоги, ингибирующие MMP и продлевающие период полувыведения.

Ключевые слова: кисспептины, агонист рецептора к кисспептинам, синтетические аналоги, рецепторы, сопряженные с G-белком, нарушение репродуктивной функции

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Kisspeptin (KP) was first discovered in 1996 [1]. mRNA was isolated from the tissue of non-metastatic melanoma, although it was not found in the tissue of metastatic tumors. This discovery highlighted kisspeptin's ability to inhibit metastasis, which led to its original name, metastin [2].

During the study of the *KISS1* gene, it was found that its transcript encodes a hydrophobic protein consisting of 145 amino acids. This protein undergoes proteolytic cleavage, resulting in peptides with a lower molecular weight, known as kisspeptins-54, -14, -13, -10, which have biological activity. The main role of kisspeptins is to control reproductive function in both sexes, and they have been shown to influence the pulsatile release of gonadotropin-releasing hormone (GnRH) in the hypothalamus [3]. In addition, many researchers have established the inhibitory property of KP on cell motility, proliferation, invasion, chemotaxis, and metastasis of tumor cells [4].

Kisspeptin peptides are characterized by variability in different species, but the C-terminus, consisting of 10 amino acids and responsible for binding to the kisspeptin receptor, KISS1R (GPR54 in animals), is conserved in both vertebrates and invertebrates [5]. Kisspeptin-10 (KP-10) is a C-terminal fragment with amino acids 45 to 54: Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2, and it is the shortest fragment capable of binding to the kisspeptin receptor with activation of the latter. The action of the 10-amino acid fragment *in vitro* is comparable to the action of the full-length 54-member polypeptide [6, 7].

Kisspeptin is mainly produced in the hypothalamus [8]. KP is synthesized in peripheral organs as well. These include the gonads, brain, pancreas, liver, small intestine, aorta, coronary arteries, and umbilical cord veins [9, 10].

It has been established that the *KISS1* and *KISS1R* genes play a role in the processes of aging, menopause, adipocyte function, and the molecular link between metabolic and reproductive processes, and may act as targets for estrogen [11, 12].

It has been found that the expression of the *KISS1* gene inhibits the activity of matrix metalloproteinases, which is a key mechanism through which *KISS1* prevents tumor metastasis. This process may also play an important role in trophoblast invasion, placental development, and perhaps gestosis [13–15].

KISS1R receptor and kisspeptin signaling pathway

The kisspeptin receptor (formerly known as GPR54, AXOR12, or hOT7T175) has a structure typical of Gq/11 proteins, and its activation triggers a signaling cascade via the phospholipase pathway [16]. Phospholipase C (PLC), activated by the Gαq subunit, catalyzes the conversion of phosphatidylinositol diphosphate (PIP2) into two second messengers: diacylglycerol (DAG) and inositol triphosphate (IP3) [17]. DAG activates protein kinase C (PKC), which in turn phosphorylates proteins in a downstream effector cascade. In addition, IP3 binds to IP3 receptors, many of which function as calcium channels (calmodulin), causing an increase in intracellular calcium levels and activation of various calcium-dependent processes in the cell [18].

This mechanism of the KP signaling cascade is primarily involved in triggering action potentials and regulating the secretion of gonadotropic hormones in the small cell nuclei of the hypothalamus [19].

Kisspeptins also initiate postsynaptic excitation of neurons in the dentate gyrus of the hippocampus in rats, indicating their significant role in learning and neurogenesis, according to studies by X. Liu et al. [20]. It is assumed that a similar mechanism underlies the vasoconstrictive properties of kisspeptins [16, 21], as well as their ability to increase the strength of heart contractions [22].

One of the mechanisms of deactivation of G protein-coupled receptors (GPRs) involves the coordinated actions of GPR kinases (GRKs) and β-arrestins-1 and -2. The interaction of the agonist with the *KISS*1R receptor triggers a process in which the heterotrimeric G protein breaks down into Gβγ and Gα-GTP subunits. For most GPRs, such as α-adrenergic receptors, the release of Gβγ subunits not only activates ion channels but also causes phosphorylation of the receptor by GPK2 kinase. Then, β-arrestins and elements of the ERK signaling pathway bind to the phosphorylated receptor via its second intracellular loop and C-terminal region, forming a complex that assembles in a clathrin-lined pit and transforms into an endosome [23]. It is important to note that for *KISS1*R, receptor desensitization also occurs in the presence of GRK2, but without phosphorylation [24]. Studies on the HEK 293 cell line (human embryonic kidney) have shown that most endosomes containing *KISS1*R return the

receptor back to the membrane rather than directing it for degradation [25].

Thus, the dynamic pool of KISS1R indicates that even temporary inactivation of these receptors does not prevent KP-10 from providing sustained stimulation of the cell. This assumption was confirmed in experiments on HEK 293 cells, where it was shown that exposure to kisspeptin-10 leads to prolonged activation of phospholipase C and protein kinase PLK enzymes, as well as an increase in intracellular calcium (Ca^{2+}) levels [24]. Moreover, H. Kroll et al. showed that kisspeptin is capable of mobilizing Ca^{2+} from intracellular depots not only during direct exposure to the peptide, but also after its removal from the culture medium [26, 27].

NATIVE AND SYNTHETIC KISSPEPTINS

Identification of key amino acids in the kisspeptin molecule that activate the receptor

Research in biochemistry and molecular biology has deepened our understanding of interaction between kisspeptins and their receptors. Determining the amino acid sequence that is necessary and enough to activate the kisspeptin receptor is one of the key aspects. In particular, it has been found that activation of the receptor by kisspeptin-10 depends on the C-terminal amino acid sequence -Phe6-Gly7-Leu8-Arg9-Phe10 [28].

A lot of data has been accumulated on synthetic agonists of the kisspeptin receptor (KISS1R), showing that certain modifications in the structure of peptides can significantly affect their ability to activate the receptor and cause biological effects, such as mobilization of intracellular calcium (Ca^{2+}). One such example is a pentapeptide with a 4-fluorinated benzene ring at Phe6, which has been shown to activate KISS1R and induce Ca^{2+} mobilization in CHO cells (Chinese hamster ovary epithelial cells), as demonstrated in studies [29, 30].

Studies have revealed that the amino acid residues Ser5 and Leu8 also play an important role in the activation of the KISS1R receptor [31]. It was found that changes in these positions can significantly affect the affinity of pentapeptides for the receptor, with the affinity of 5-amino acid peptides being significantly lower than their 10-amino acid counterparts. These results highlight the importance of the precise structural configuration of peptides for their ability to interact with and activate the KISS1R receptor, which is important for the development of new therapeutic agents targeting this receptor pathway.

Experiments replacing individual amino acids in this sequence showed that replacing Phe6, Leu8, and Phe10 with alanine (Ala) and with dextrorotatory enantiomers results in a loss of affinity for the receptor. These findings indicate that the specific interaction of kisspeptin and the receptor greatly depends on steric factors, such as amino acid side chain orientation and overall peptide flexibility [32, 33].

Kp-13 appeared to have a helical structure with Asn7 to Phe13, and the receptor binding site is formed by Phe9, Arg12, and Phe13 [34].

A synthetic decapeptide with a dextrorotatory enantiomer Phe1 ([dY]1 NWNSFGLRF-NH2) also showed lower affinity for the receptor *in vitro*, contrary to the previously mentioned study [33]. Differences between the two studies can be explained by various experimental methods. In the first case, a model of yeast transfected with the *KISS1R* gene and analysis of the activity of the *lac*Z reporter gene were used, which allows assessing the functional activity of the receptor under conditions close to natural ones. In the second case, a method of hybridization of a radioactively labeled peptide with membrane proteins of *KISS1*R-transformed CHO cells was used, which provides information about the direct interaction of the peptide with the receptor, but may not fully reflect its biological activity *in vivo*.

Despite differences in affinity, intraperitoneal administration of this analogue in a nanomolar dose to C57Bl/6 mice led to a significant increase in plasma testosterone levels. This indicates that when the affinity for the receptor is reduced *in vitro*, the analogue can be effective in stimulating the secretion of gonadotropic hormones *in vivo*, which emphasizes the importance of conducting studies on living organisms to evaluate the pharmacological activity of substances [32].

In order to evaluate the contribution of each side functional group of KP-10 to the agonistic activity of the molecule in relation to KISS1R and its interaction with the plasma membrane, a series of structural

analyses were performed, along with functional analysis, using alanine scanning (sequential replacement of each of the peptide amino acids with alanine). For this purpose, Gq/11-linked protein kinase C and a specific reporter system (c-fos-luc) were used in the functional analysis. Analogues with alanine substitutions at Tyr1, Trp3, or Ser5 showed similar activity to native kisspeptin-10, whereas alanine substitutions at Asn2, Asn4, Phe6, Gly7, Leu8, or Arg9 caused a clear decrease in agonist activity [31]. In particular, two analogues, F10A and the non-amidated form (NH2·OH), did not exhibit GPR54 signaling activity. Similarly, it has been previously reported that the C-terminal quintet and amide group of kisspeptin-10 are important for specific binding to GPR54 and potent agonistic activity [35].

Thus, these results emphasize the importance of precise amino acid sequence and spatial configuration for the binding of kisspeptin to its receptor, which may be particularly important for the development of new drugs aimed at regulating reproductive function and other processes controlled by kisspeptins.

Comparison of kispepitin-10 and kispepitin-54

KP-10 and KP-54 are the two most commonly used forms of kisspeptin in research. It has been found that KP-10 undergoes rapid metabolism in mouse serum, with more than 50% of the peptide metabolized within the first minute after administration. This rapid breakdown of KP-10 may be associated with the presence of metabolically sensitive amino acid residues such as tyrosine (Tyr) and arginine (Arg) in its structure. These amino acids may make the peptide particularly vulnerable to the action of peptidases, enzymes that break down peptide bonds [36].

Native (natural) KP is metabolically unstable in blood and is hydrolyzed by various serum proteases and metalloproteinases, such as MMP-2 and MMP-9 [37]. The matrix metalloproteinase family is a group of structurally related zinc-containing endopeptidases that break down basement membranes and the extracellular matrix under physiological and pathological conditions [38, 39]. A number of studies have shown that the activity of type 2 or type 9 matrix metalloproteinases is suppressed by the protein kisspeptin. It is important to note that active MMPs can cleave the peptide bond between Gly 51-Leu 52 in the KP-54 protein sequence. As a result, three amino acids are cleaved from the N-terminus of the peptide, leading to the inactivation of KP-54, i.e., it can no longer perform its biological functions [40].

The half-life of KP-10 in humans is approximately 4 minutes [41]. This means that KP-10 is rapidly metabolized and eliminated, which may limit its therapeutic use without repeated or continuous administration.

Unlike KP-10, KP-54, consisting of 54 amino acids, is characterized by a longer half-life (approximately 28 minutes) [42]. The increased stability of KP-54 enhances its potential for clinical use, since it provides prolonged action with a single administration.

These differences in the pharmacokinetics of KP-10 and KP-54 may influence their selection in research and potential therapeutic applications, especially in the context of regulating reproductive function and other physiological processes involving kisspeptins. The pharmacokinetic properties of KP-54 make it more suitable for bolus administration than KP-10. A bolus of KP-54 causes a moderate increase in gonadotropin levels in healthy women in the follicular phase of the menstrual cycle, whereas a similar administration of KP-10 does not produce the same effect [41].

However, when KP-10 and KP-54 are administered continuously intravenously in equimolar doses to healthy men, they cause a similar increase in gonadotropin levels, indicating their effectiveness with this method of administration [43]. At the same time, gonadotropin levels (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)) after administration of these kisspeptins are lower than after administration of gonadotropin-releasing hormone (GnRH), which may reflect differences in their mechanisms of action. Kisspeptins act at the level of the hypothalamus, stimulating the release of GnRH, while GnRH directly stimulates the pituitary gland to secrete gonadotropins.

Competitive binding experiments have shown that KP-54 and KP-10 have the same affinity for human and rat kisspeptin receptors, as confirmed by Ki (1.45–2.33 nM) and EC50 (4.13–5.47 nM) values [6]. However, another study showed that KP-10 and KP-15 are five times more effective than KP-54, while KP-9 was less active [8]. The effectiveness of these kisspeptins was also proven by using the FLIPR (FLuorometric Imaging Plate Reader) method. This method allows

recording rapid changes in intracellular calcium (Ca^{2+}) concentration as an indicator of receptor activation. The study revealed a clear dose-dependent activity: at a concentration of KP 10^{-11} M, there was no significant release of Ca^{2+}, while in the range of 10^{-9}–10^{-8} M, maximum activation of *KISS1*R was observed [36].

Short KP analogues have a potential therapeutic effect, however, like many other peptide hormones, they are subject to rapid enzymatic degradation, which limits their use, since high doses and/or frequent administration are required to achieve a therapeutic effect, which may be inconvenient for patients and may increase the risk of side effects.

Thus, the development of KP analogues that activate the kisspeptin receptor and are resistant to or inhibit the activity of matrix metalloproteinases may open up prospects for creating new antitumor drugs or replacing hormone therapy with already known hormones.

Modifications of kisspeptin that Improve its stability in vivo

To improve the metabolic stability of KP *in vivo*, researchers can use various approaches, including:

- *modification of the amino acid sequence.* Changing certain amino acids in the peptide can make it less vulnerable to protein-cleaving enzymes.
- *introducing chemical modifications.* This includes incorporating phosphonic acids into the composition of KP or using synthetic amino acids that can increase its stability.
- *reducing the length of the amino acid sequence.* Shortening the amino acid sequence by removing sections that are easily cleaved by proteases (e.g., Tyr and Arg residues) can increase the peptide's resistance to metabolic breakdown in the blood and tissues.

Most research has focused on modifying the cleavage site.

It is known that peptides containing Arg are good substrates for trypsin-like proteases. Kisspeptin analogues in which Arg is replaced by neutral L-amino acids such as alanine (Ala), leucine (Leu), norleucine (Nle), and citrulline (Cit), which were supposed to prevent recognition and cleavage by trypsin, critically affected the activity of the molecule, reducing it by 21–110 times [44]. Thus, it is not advisable to replace Arg at position 53, as the basic amino acid at this position appears to be necessary for the biological activity of the peptide.

Replacing an L-amino acid with the corresponding D-amino acid sometimes leads to an improvement in the biological activity of the peptide, as it changes the conformational properties of the peptide and increases its resistance to enzyme degradation [45], whereas no such effect has been observed with Arg.

Arg53 was modified in one study by methylating the guanidino group of arginine Arg (Me). During subsequent evaluation of its properties, it was found that the Nx-methylarginine analogue has stronger agonistic activity than KP-10 and is resistant to trypsin cleavage between positions 53 and 54 [46].

Phosphinic kisspeptin

Based on the primary structure of KP-10, two pentapeptides were developed and synthesized to improve the stability of the peptide [47]. The peptide bond between Gly-Leu was replaced with a phosphinic acid fragment $-PO_2-CH_2$. Synthetic peptides containing a phosphinic acid fragment substitution for the peptide bond are called KP-phosphinic peptides.

To verify the functional properties of the new synthetic peptides, their ability to bind and activate the kisspeptin receptor was evaluated. Human kidney cell culture HEK293 was selected as a model object for testing. This choice was due to the fact that HEK293 cells express the receptor for kisspeptins, which is important for embryonic kidney morphogenesis and glomerular development [48]. They also have low basal ERK1/2 phosphorylation activity (extracellularly regulated kinases 1 and 2, which are part of the MAPK cascade that plays an important role in transmitting signals from receptors on the cell surface to the nucleus).

The agonistic activity of KP phosphinic peptides against the kisspeptin receptor was evaluated by measuring the stimulation of ERK1/2 phosphorylation. The results showed that the phosphinic kisspeptin R-isomer (PKPR) is capable of binding with and activating the KISS1R receptor, as confirmed by a reliable calcium response at a concentration of 10 μM.

Phosphine peptides are known as potent and selective inhibitors of various proteases, such as MMP [49, 50], since their chemical structure mimics the intermediate transition state formed during peptide hydrolysis by proteases. It has been shown that PKPR

at a final concentration of 10 μM inhibited MMP-2 activity by 36%, while none of the synthesized phosphine peptides inhibited MMP-9 activity.

Clinical application of synthetic kisspeptins in treating reproductive disorders and oncology

Synthetic kisspeptins, which are peptides derived from the natural hormone kisspeptin, are used in clinical practice as potential therapeutic agents for treating various conditions associated with the reproductive and endocrine systems. The main areas of clinical application of kisspeptins are listed below.

1. Treatment of reproductive disorders

Hypogonadotropic hypogonadism: Kisspeptins can be used to stimulate GnRH release, which in turn activates the production of gonadotropins (LH and FSH) and helps normalize sex hormone levels. This may be particularly useful for treating patients with hypogonadotropic hypogonadism, including conditions such as Kallmann syndrome [13, 51].].

2. Treatment of menstrual disorders and infertility

Induction of ovulation: Kisspeptins can be used to induce ovulation in women with ovulatory disorders, which may help in treating certain forms of infertility and may be used in *in vitro* fertilization (IVF) programs [52, 53].

Vitrification of ovarian tissue: Kisspeptins can be used as an agent to improve the quality of the cryopreservation environment by improving follicle maturation and increasing their viability after thawing [54].

Hyperprolactinemia: Administration of kisspeptin leads to an increase in LH levels in patients with both normal (in the case of hypothalamic amenorrhea) and elevated prolactin levels [55]. C.N. Jyasena et al. reported a tenfold increase in LH levels and a 2.5-fold increase in FSH levels after subcutaneous administration of kisspeptin-54 at a dose of 6.4 nmol/kg in women with amenorrhea against a background of hyperprolactinemia [56]. The number of studies confirming this relationship continues to grow. Thus, a positive effect was demonstrated after the administration of kisspeptin-54 to patients with hypothalamic amenorrhea, manifested at the onset of preovulatory LH levels [57].

3. Regulation of puberty

Delayed puberty: The administration of kisspeptins can stimulate the onset of puberty in children with delayed puberty [58].

Premature puberty: In theory, kisspeptin antagonists may be used to control or delay premature puberty, although this area requires further research [59].

4. Research in oncology

Tumor metastasis: Based on the role of the *KISS1* gene in suppressing tumor metastasis, kisspeptins may be investigated as potential agents for preventing the spread of cancer cells [4, 60].

Kisspeptins, particularly KP-10, are the subject of intensive clinical trials, reflecting their significant therapeutic potential. According to the clinicaltrials.gov registry in July 2025, 19 studies were completed to investigate the use of these peptides for treating such conditions as infertility, hypogonadotropic hypogonadism, and diabetes mellitus[1]. The results confirm the potential of kisspeptins as therapeutic agents capable of modulating key physiological and pathological processes.

Currently, 12 other projects are actively ongoing, with a particular focus on the role of kisspeptins in carcinogenesis. These findings reflect the broadening of scientific interests and indicate their potential application in oncology. In-depth study of the modes of action and therapeutic potential of these peptides may open up new perspectives in treating various diseases, including those currently considered intractable.

To date, only two groups of researchers have taken steps in medical chemistry to develop kisspeptin receptor agonists with an improved pharmacological profile *in vivo* compared to native KP. The first group produced a series of decapeptide analogues of KP-10, in which one amino acid was replaced by an enantiomer or another amino acid, and the best analogue was tested *in vivo* for its ability to stimulate the gonadotropic axis [61].

The second group performed several modifications of the KP-10 sequence, resulting in several degradation-resistant analogues. The aim of this study was to reduce GnRH secretion by desensitizing KISS1R with an extremely long-acting agonist and, consequently, to reduce circulating gonadotropins and testosterone to castration levels, which is relevant for hormone-dependent cancer therapy [62, 63]. However, depending on the dosage regimen, an analogue of this type can also be used to stimulate the reproductive system.

[1] https://clinicaltrials.gov/search?cond=kisspeptin.

Thus, native kisspeptin is a natural ligand for the GPR54 (or KISS1R) receptor, which plays a key role in activating gonadotropin-releasing hormone (GnRH), which in turn stimulates gonadotropin secretion and regulates reproductive function. Native kisspeptin is effective in initiating this cascade, but its use is limited due to rapid degradation and low bioavailability. Synthetic kisspeptin analogues, including those with modifications to improve stability, have been developed to overcome these limitations. Modifications may include amino acid substitutions, the addition of protective groups that slow degradation, or changes to the molecular structure to improve receptor binding. These changes can significantly increase the half-life of the peptide in the blood, improve its ability to cross biological barriers, and enhance overall efficacy. Kisspeptin-based therapy may be productive in the treatment of malignant tumors, diseases associated with metabolic disorders, delayed puberty, and infertility. However, a short half-life limits the therapeutic potential of this molecule. Further research is needed to determine optimal dosages, administration regimens, and duration of therapy with kisspeptins, as well as to fully understand their potential side effects and interactions with other drugs.

ADDITIONAL INFORMATION

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