ARTICLE / INVESTIGACIÓN

Beyond reproduction: Exploring the Non-Canonical roles of the Kisspeptin System in Diverse Biological Systems

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Abstract: G protein-coupled receptors are integral membrane proteins in cell signaling processes. Activation of G protein-coupled receptors by specific agonists promotes the activation of different G-proteins, activating different intracellular signaling pathways, including adenylate cyclase activation and intracellular calcium release. One of the G protein-coupled receptors studied is the kisspeptin receptor, which regulates reproduction and gonadotropin secretion. However, recent studies have shown that kisspeptin and its receptor have non-canonical roles in cell signaling and several biological systems. In the present review, we will present these different functions exerted by the kisspeptin system in different biological systems, such as the central nervous system, the cardiovascular system, and the immune system, as well as the role of this system in pathologies such as preeclampsia, diabetes, and cancer. Understanding their non-canonical roles in cell signaling may have important implications in developing new therapies for various diseases.

Key words: Kisspeptin-1 Receptor, Kisspeptins, G-protein coupled receptor, Signal Transduction, Cancer, Diabetes Mellitus, Preeclampsia.

Introduction

Kisspeptins are a family of related peptides identified as the natural ligands of the G protein-coupled receptor (GPCR) GPR54[1-3], also known as the kisspeptin receptor (KISS1R). The physiological ligand for the KISS1R receptor was identified by several groups in 2001[2-4] and is encoded by the KISS1 gene, which produces a 145 amino acid protein, Kisspeptin54 (KP-54), also known as metastin (Figure 1). The C-terminal region of KP-54 is responsible for binding to the receptor, and this region is the most conserved among different species. The peptides in this 10-, 13- and 14-amino acid portion (KP-10, KP-13, and KP-14) exhibit similar activities at the Kiss1R receptor in vitro assays[2-4].

The kisspeptin-KISS1R system plays an essential role in the neuroendocrine control of the reproductive axis5. However, in recent years, the kisspeptin system has also been found to be involved in various biological processes non-related to reproduction. These non-canonical roles of kisspeptin have been identified in multiple methods, including the cardiovascular system[6], central nervous system[7], immune system[8], preeclampsia[9], diabetes[10], and cancer[11].

Non-canonical signaling refers to biological effects that occur through pathways other than classical GPCR signaling. In the case of the kisspeptin system, these effects may be mediated by the activation of sex hormone receptors[12], translation factors[13], and ionic channels[14]. It has also been shown that kisspeptin can interact with other signaling systems, such as the insulin signaling system and the insulin-like growth factor (IGF) system[15]. The precise mechanisms

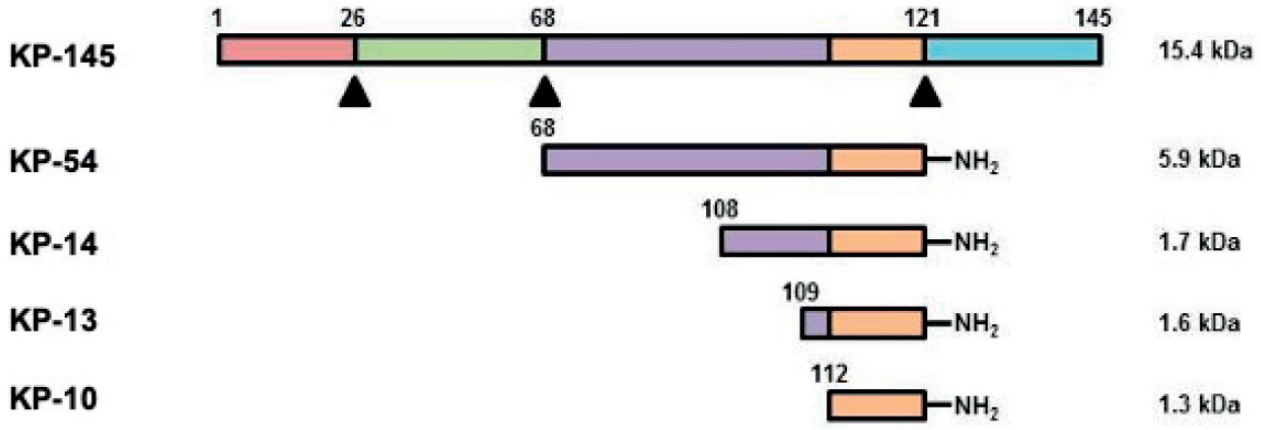

Figure 1. Production of kisspetins. The primary protein product of the KISS1 gene is cleaved (triangles) to produce small amidated peptides (kisspeptins, Kp) capable of binding to the GPR54 receptor. All peptides containing the same C-terminal portion are biologically active. Source: Author.

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of kisspeptin non-canonical signaling and its physiological effects have yet to be fully elucidate and are still under study.

In this review, recent findings on the non-canonical roles of kisspeptin in various biological systems, including the cardiovascular system, central nervous system, preeclampsia, immune system, diabetes, and cancer, will be presented. In addition, possible underlying mechanisms of non-canonical kisspeptin signaling and their potential clinical significance will be discussed.

Non-Canonical Signaling of Kisspeptins

Studies have revealed that Kisspeptins, primarily acting via the KISS1R receptor, activate the Gq/11 protein, increasing intracellular calcium through PLC activation[2]. Also, kisspeptins can activate critical non-canonical pathways, allowing us to understand the complexity of the signaling processes. One of the most studied examples of non-canonical kisspeptin signaling is the activation of the ERK1/2 signaling pathway through the direct binding of kisspeptin to the MET tyrosine kinase receptor[16], and this signaling pathway has been implicated in promoting progesterone secretion. Also, according to a study conducted by Kim and Cho[13], the activation of EIF2AK2 induced by kisspeptin may require the presence of RhoA. This suggests that the signaling pathway responsible for the effects of kisspeptin may be illustrated by the sequence KISS1R/Gq/11/p63RhoGEF/RhoA/EIF2AK2. This signaling pathway leads to inhibit cancer growth and metastasis.

In addition, it has been shown that kisspeptin can activate the Ca^{2+} mobilization and cAMP reduction levels through interaction with receptors for other ligands, such as Neuropeptide FF receptors (NPFFR1 and NPFFR2)[17], with highly potent activity leading to the possible localization of a secondary kisspeptin receptors such as NPFFRs (Figure 2.).

In summary, non-canonical cell signaling of the kisspeptin system is an emerging area of research that may have essential implications in regulating physiological and pathological function. Although several non-canonical signaling pathways activated by kisspeptin have been identified, further studies are needed to understand their role in regulating physiology and pathology.

Non-Canonical Roles of Kisspeptins

Kisspeptins and the Cardiovascular System

The kisspeptin system is a peptide signaling important in regulating reproduction, appetite, metabolism and energy homeostasis[2-4]. In addition, the kisspeptin system has also been shown to be involved in regulating cardiovascular function.

Kisspeptin and its receptor KISS1R can be found in endothelial cells, vascular smooth muscle, and other cardiovascular tissues, including the aortic artery[18]. In the isolated human coronary artery and umbilical vein, it was observed that KP-10, KP-13, and KP-54 act as powerful vasoconstrictors. The response of these tissues to KP was similar to that of angiotensin (AngII) in the coronary artery, as reported in that study[18].

Also, in 2011, Maguire et al. showed that kisspeptins are a potent positive inotrope in the atria of humans, rats, and mice[19]. KP-10 vascular effects are considered significant due to hypertension and edema as symptoms of preeclampsia in late-term pregnancies, which subside after delivery.

In summary, understanding the potential "off-target" cardiovascular effects can guide the development and usage of kisspeptin-derived treatments, such as improved analogs and antagonists with increased efficacy[21].

Kisspeptins and Preeclampsia

Preeclampsia is a pregnancy complication that involves high blood pressure and dysfunction of the body's endothelial cells. Studies suggest that changes in the levels of

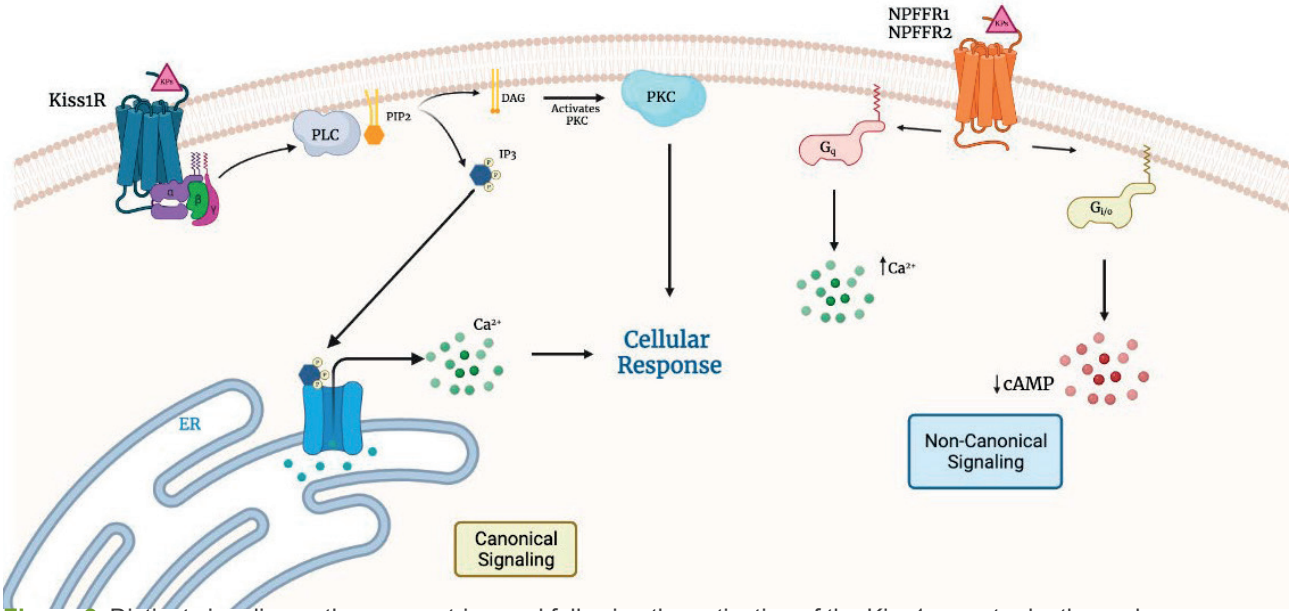

Figure 2. Distinct signaling pathways are triggered following the activation of the Kiss1 receptor by the endogenous agonist's KPs. The canonical KISS1 receptor signal transduction pathways triggered by the endogenous agonist KPs include coupling to the Gq-protein with the activation of PLC, which processes the membrane PIP2 to produce IP3 and DAG. IP3 interacts with IP3 receptors (IP3R) at the endoplasmic reticulum and releases Ca^{2+}, which, together with DAG, leads to PKC activation. In the non-canonical signaling pathway, KPs bind to NPFFR receptors, activating two G_{q-} and $G_{i/o-}$ dependent signaling that promote an increase in intracellular calcium and a decrease in cAMP concentration.

KISS1 and KISS1R, both at the mRNA and protein levels, may be responsible for causing preeclampsia. These changes lead to a decrease in KISS1 expression and an increase in KISS1R expression compared to a normal, healthy pregnancy[22]. Kisspeptin is expressed in the placenta and has been shown to play an essential role in regulating fetal growth and development[23], as well as in angiogenesis and placental endothelial function[23,24]. In addition, lower levels of plasma kisspeptin-10 have been associated with more severe forms of the disease[25].

Kisspeptin may play a role in the development of preeclampsia by inhibiting the growth of new vessels from placental vessels[24]. A clinical study demonstrated that women with preeclampsia had lower levels of plasma kisspeptin-10, which was inversely correlated with the severity of their condition. Maternal plasma KP-10 levels were also associated with estimated fetal weight during the second and third trimesters[26]. Another study found that kisspeptin levels at 16 weeks in maternal plasma were positively correlated with the birthweight of fetuses in uncomplicated pregnancies[27]. The results indicate that plasma levels of kisspeptin may function as a biomarker of insufficient blood flow to the uterus and placenta, along with limited fetal development within the uterus, lead to restricted growth.

Kisspeptins and the Central Nervous System

Several lines of evidence indicate kisspeptin directly affects Gonadotropin hormone-releasing Hormone (GnRH) neurons. Firstly, most GnRH neurons express KISS1R[28]. Furthermore, the fibers of KISS1R are close to GnRH neurons and stimulate the release of gonadotropin-releasing hormone by activating multiple ion channels through a pathway dependent on phospholipase C and calcium[29]. Thirdly, kisspeptin can directly depolarize and increase the firing rates of GnRH neurons *in vitro*[28]. It is important to note that kisspeptin may not only act through traditional synaptic mechanisms to stimulate GnRH secretion but also directly in a non-synaptic manner, especially in the median eminence[30]. Increasing evidence suggests that kisspeptin also affects intermediary neurons, such as GABAergic cells, to regulate GnRH secretion[31,32].

Additionally, the study conducted by Khonacha et al. demonstrated that KP-13 can enhance spatial memory consolidation and retrieval. Also, when administered in the presence of Amiloid β (Aβ), KP-13 significantly improved reference memory impairment caused by Aβ. These findings suggest that KP-13, as a neuropeptide, may possess neuroprotective properties against amyloid-beta-induced pathology and has the potential to enhance spatial memory[33].

Kisspeptins and the Immune System

Due to the expression of kisspeptin receptors on various immune system cells[2-4], it has been proposed that kisspeptin, in conjunction with other pregnancy hormones and proteins, has the potential to regulate immune responses. Also, kisspeptin may play a role in regulating cytokines, which are proteins that control the immune response and can be regulated through modulation of their production. In particular, it has been shown that kisspeptin can increase the production of anti-inflammatory cytokines such as interleukin-10 (IL-10) and decrease the production of proinflammatory cytokines such as interleukin-17A (IL-17A)[8].

Studies on the immune system response to kisspeptin have covered how the hormone regulates CD4+T lymphocytes through molecular mechanisms[35]. By binding to KISS1R, kisspeptin increases intracellular cAMP concentrations, boosting iTreg production and the quantity of these cells in the culture. The heightened cAMP also activates cAMP response element binding protein (CREB) and MAPK/ERK (MEK1/2)[36], which helps CD4+ lymphocytes differentiate into iTreg and reduces RORC expression. The capacity of [Ca2+] governs the control of the cAMP-dependent activity of kisspeptin in lymphoid cells I to trigger protein kinase A (PKA) through Ca2+/CaM, Ca2+/CaM dependent protein kinase 2 (CaMKK2), and AMP-activated protein kinase (AMPK)[37]. PKA, in turn, inhibits mTOR[38], which activates RORC transcription[39] and phosphorylates CREB[40]. The role of kisspeptin in coordinating reproductive and immune functions may help to discover new mechanisms of this control system.

Kisspeptins and Diabetes

Diabetes is a long-term condition marked by high glucose levels in the blood. This occurs either because the pancreas does not produce enough insulin or because it is resistant to the effects of insulin, a hormone responsible for regulating blood glucose levels. The kisspeptin system has been interested in diabetes because it regulates energy metabolism and pancreatic function[10].

It has been shown that kisspeptin and its receptor KISS1R are expressed in the pancreas, the organ responsible for the production of insulin[4]. In particular, it has been demonstrated that kisspeptin administration can increase insulin production in animal models of type 2 diabetes (DM2)[41].

The role of KP in DM2 indicates that KP-10 may benefit diabetic patients, as it has been found to increase testosterone secretion in men with DM2 and central hypogonadism[42]. Animal studies have also shown that KP may regulate insulin secretion[43], but *in vivo*, experiments are necessary to explore its effects on peripheral organs that control metabolism.

In summary, pancreatic function, insulin production, energy metabolism, and insulin sensitivity are significantly influenced by the regulation of the kisspeptin system. However, the effects of kisspeptin on pancreatic function may be contradictory, and additional research is required to investigate the relationship between KP and insulin in DM2 patients.

Kisspetins and Cancer

The regulation of cancer cell proliferation and invasion in various types of cancer has been linked to the kisspeptin system and its receptor, KISS1R. Studies have demonstrated that kisspeptin inhibits cell proliferation and invasion in breast[44], prostate[45], ovarian[46], lung[47], and gastric[48] cancers.

In breast cancer, kisspeptin and KISS1R expression have been shown to correlate inversely with the degree of tumor malignancy, suggesting that the kisspeptin system may have a role in suppressing invasion and metastasis in this type of cancer[49]. In addition, it has been shown that kisspeptin administration can inhibit cell proliferation and tumor formation in animal models of breast cancer[50]. In prostate cancer, it has been reported that kisspeptin and KISS1R expression is reduced in advanced tumors[45], suggesting that the kisspeptin system may also have a role in suppressing invasion and metastasis in this type of cancer. In ovarian cancer, high concentrations of KISSR lead to increased inhibition of cell migration[51] and hypersensitization of cells to chemotherapy[52]. It has also been shown to act

as a suppressor of metastasis and suppresses NF-kB and MMP9 expression[53].

In gastric cancer, the kisspeptin system also has metastasis suppressor activity, as it inhibits cell growth, proliferation, and invasion[48].

To summarize, the kisspeptin system seems to significantly inhibit the spread and metastasis of various cancer types, indicating its potential as a therapeutic target for cancer treatment. However, additional research is necessary to understand better the kisspeptin system's role in cancer progression and its efficacy in treating diverse cancer types.

Conclusions

Investigating the kisspeptin system is crucial for both its reproductive and non-reproductive functions. Regarding reproduction, kisspeptin is essential in regulating the hypothalamic-pituitary-gonadal axis, which controls puberty, menstrual cycles, fertility, and overall reproductive health. Understanding the mechanisms behind this regulation can provide valuable insights into reproductive disorders and offer new avenues for treatment.

Moreover, the kisspeptin system has been found to play non-reproductive roles in various physiological systems (Table 1.), including diabetes, metabolism, memory, cardiovascular function, preeclampsia, and cancer. These findings suggest that kisspeptin has a broader scope and is vital in maintaining organismal homeostasis.

Therefore, studying the non-canonical roles of kisspeptin can provide a more comprehensive understanding of its function and lead to the development of therapies and treatments for various health issues, such as obesity, diabetes, cardiovascular disorders, and stress.

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Conflicts of Interest

The author declares no conflict of interest.

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Tissue	Physiologic / Pathophysiologic role	Reference
Placenta	The Kisspeptin system may be involved in placental vascularization and in modulating the production of hormones involved in the maintenance of pregnancy, such as hCG (human chorionic Gonadotropin) and progesterone.	[23]Hu, 2019
Pituitary Gland	Kisspeptins act on its specific receptor (Kiss1R) to stimulate the release of gonadotropin-releasing hormone (GnRH).	[54] d'Anglemont de Tassigny, 2008
Pancreas	Kiss1R overexpression shows evidence of association of Kiss1R with a reduction in the invasive and migratory ability of pancreatic cancer cells[55]. Also, studies suggest that kisspeptin may influence insulin secretion and insulin sensitivity[10].	[55]Wang, 2016 [10]Dudek, 2019
Liver	Using high-fat diet-fed mice, it was demonstrated that a deletion of hepatic Kiss1R exacerbated hepatic steatosis. In contrast, enhanced stimulation of Kiss1R protected against steatosis and decreased fibrosis using a diet-induced mouse model of Nonalcoholic fatty liver disease (NASH). These findings establish Kiss1R as a therapeutic target for treating NASH.	[56]Guzman, 2022
Brain	KP-13 shows potential neuroprotective effects against amyloid-beta-induced pathology and improves spatial memory.	[33]Khonacha, 2022
Aorta, Coronary Artery, Umbilical Vein	The Kisspeptin system signaling promotes vasoconstrictor effects.	[18]Mead, 2007
Prostate	Kisspeptin expression levels are significantly higher in benign prostate tissues compared to primary and metastatic prostate carcinomas. Thus, it has been suggested that Kisspeptins expression in the tumor may serve as an essential prostate cancer marker that can be used to monitor the conversion of a benign condition to malignancy.	[50]Cho, 2009
Breast	The KP10/Kiss1R signaling increased MMP-9 activity, and the cytoskeletal changes induced by this factor enhanced the motility of breast cancer cells.	[49]Zajac, 2011
Ovary	The overexpression of Kiss1R in ovarian carcinoma suppresses the expression of MMP-9 and NF-κB, factors linked to cancer formation, growth and migration	[57]Ji, 2013
Gastric	Overexpression of the gene KiSS-1 inhibits cell growth, proliferation and invasion in gastric carcinoma cells, proving the antimetastatic potential of kisspeptin. It has also been suggested that KiSS-1 expression as a prognostic marker can be employed to anticipate survival outcomes.	[48]Ergen, 2012

Table 1. Physiological and pathophysiological roles of the Kisspeptin system in different tissues.

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