



Kisspeptin a potential therapeutic target in treatment of both metabolic and reproductive dysfunction

Joanna Helena Sliwowska¹ | Nicola Elizabeth Woods² |
Abdullah Rzgallah Alzahrani^{2,3} | Elpiniki Paspali⁴ | Rothwelle Joseph Tate² |
Valerie Anne Ferro²

¹Department of Veterinary Medicine and Animal Sciences, Laboratory of Neurobiology, Poznan University of Life Sciences, Poznan, Poland

²Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

³Department of Pharmacology and Toxicology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

⁴Department of Chemical Engineering, University of Strathclyde, Glasgow, UK

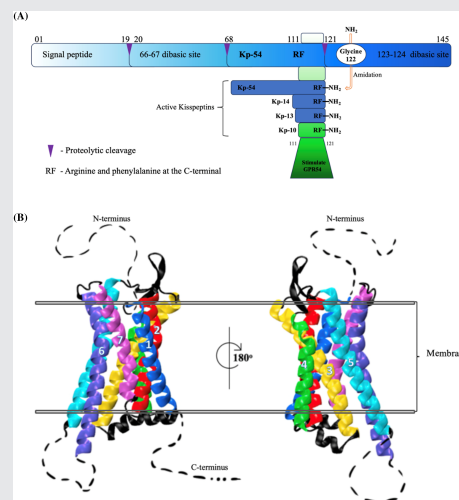
Correspondence

Valerie Anne Ferro, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, UK.
Email: v.a.ferro@strath.ac.uk

Funding information

Saudi Arabia Cultural Bureau in London; Biotechnology and Biological Sciences Research Council, Grant/Award Number: BB/F017642/1; Uniwersytet Przyrodniczy w Poznaniu, Grant/Award Numbers: 506-511-09-00, 2015/17/B/NZ4/02021; University of Strathclyde

Graphical Abstract



Highlights

- Kisspeptins (KPs) were first discovered to have antimetastatic action. Historically, a role in reproduction was demonstrated. Today, there is growing experimental and clinical evidence that KPs and their receptors regulate metabolism.
- Disruption of KP and receptor interaction provides an interesting approach to treating metabolic conditions, as well as reproductive disorders.
- Clinical trials have focused mainly on treating reproductive dysfunctions; however, greater understanding of the biology and mechanisms of action of KPs is being used in the therapeutic armory against insulin-related dysfunctions.
- Linkage between reproduction and metabolism via the KP system also allows for therapeutic targeting.

Joanna Helena Sliwowska and Nicola Elizabeth Woods these authors are Joint first author.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Authors. *Journal of Diabetes* published by Ruijin Hospital, Shanghai Jiaotong University School of Medicine and John Wiley & Sons Australia, Ltd.



Kisspeptin a potential therapeutic target in treatment of both metabolic and reproductive dysfunction

Joanna Helena Sliwowska¹ | Nicola Elizabeth Woods² |
Abdullah Rzgallah Alzahrani^{2,3} | Elpiniki Paspali⁴ | Rothwelle Joseph Tate² |
Valerie Anne Ferro²

¹Department of Veterinary Medicine and Animal Sciences, Laboratory of Neurobiology, Poznan University of Life Sciences, Poznan, Poland

²Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

³Department of Pharmacology and Toxicology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

⁴Department of Chemical Engineering, University of Strathclyde, Glasgow, UK

Correspondence

Valerie Anne Ferro, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, UK.
Email: v.a.ferro@strath.ac.uk

Funding information

Saudi Arabia Cultural Bureau in London; Biotechnology and Biological Sciences Research Council, Grant/Award Number: BB/F017642/1; Uniwersytet Przyrodniczy w Poznaniu, Grant/Award Numbers: 506-511-09-00, 2015/17/B/NZ4/02021; University of Strathclyde

Abstract

Kisspeptins (KPs) are proteins that were first recognized to have antimetastatic action. Later, the critical role of this peptide in the regulation of reproduction was proved. In recent years, evidence has been accumulated supporting a role for KPs in regulating metabolic processes in a sexual dimorphic manner. It has been proposed that KPs regulate metabolism both indirectly via gonadal hormones and/or directly via the kisspeptin receptor in the brain, brown adipose tissue, and pancreas. The aim of the review is to provide both experimental and clinical evidence indicating that KPs are peptides linking metabolism and reproduction. We propose that KPs could be used as a potential target to treat both metabolic and reproductive abnormalities. Thus, we focus on the consequences of disruptions in KPs and their receptors in metabolic conditions such as diabetes, undernutrition, obesity, and reproductive disorders (hypogonadotropic hypogonadism and polycystic ovary syndrome). Data from both animal models and human subjects indicate that alterations in KPs in the case of metabolic imbalance lead also to disruptions in reproductive functions. Changes both in the hypothalamic and peripheral KP systems in animal models of the aforementioned disorders are discussed. Finally, an overview of current clinical studies involving KP in fertility and metabolism show fewer studies on metabolism (15%) and only one to date on both. Presented data indicate a dynamic and emerging field of KP studies as possible therapeutic targets in treatments of both reproductive and metabolic dysfunctions.

KEYWORDS

diabetes mellitus, KISS1/Kiss1, KISS1R/Kiss1r, kisspeptin, obesity, reproduction

Joanna Helena Sliwowska and Nicola Elizabeth Woods these authors are Joint first author.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Authors. *Journal of Diabetes* published by Ruijin Hospital, Shanghai Jiaotong University School of Medicine and John Wiley & Sons Australia, Ltd.

1 | INTRODUCTION

1.1 | Emerging functions of kisspeptins (KPs)

The role of kisspeptins (KPs) was first investigated in the field of oncology as an antimetastatic factor, known as metastin, later in reproductive biology, and more recently in the control of metabolic functions.^{1–3} Their effect has an impact throughout the body, including the brain, reproductive organs, pancreas, cardiovascular system, and kidneys.⁴

The unraveling of the complexities of this family of peptides in the regulation of reproduction began with the concept of the existence of hypothalamic releasing hormones and subsequent gonadotropin-releasing hormone (GnRH).⁵ However, it was recognized that GnRH was not the sole regulator of reproductive function, particularly as satisfactory explanations could not be found for the pulsatile release of GnRH and the onset of puberty. Hence, some other factor(s) had to be involved. Growing evidence from genetic loss-of-function variant studies in the early 2000s led to the understanding of the involvement of KPs in GnRH release⁶ and the regulation of puberty.^{7–9} This was surprising because knowledge of KP and the *KISS1* gene was already established in an antimetastasis role.¹⁰

1.2 | KP and its receptor

The gene for KP was named *KISS1* as it was first cloned in Hershey, Pennsylvania, a city known for making chocolate kisses.¹¹ The 54 amino acid peptide, Kisspeptin-54 (Kp-54), is the major known fraction. Figure 1 shows how different fractions of KPs are derived from the first transcription of *KISS1*, which consists of 145 amino acids (pre-pro-kisspeptin) that are then proteolytically cleaved to produce Kp-54 and the less common Kp-14, Kp-13, and Kp-10 peptides.¹⁴

KISS1 mRNA is widely expressed in numerous tissues including the placenta,¹⁵ testis,¹⁶ ovaries,¹⁷ liver,¹⁸ pancreas,¹⁹ small intestine,⁷ and crucially in the central nervous system (CNS), in particular the hypothalamus, where *KISS1* is a key regulator in fertility.^{20,21} It is important to note that in the hypothalamus, expression of kisspeptin and its receptor varies considerably depending on the species and gender and throughout the life stage of an organism.²² Aligned with its role in the development and regulation of cancers, *KISS1* and its receptor are also found in a number of human cancers including breast and prostate, where they can serve as both prognostic biomarkers and therapeutic targets.²³ The receptor is

classified as a G-protein coupled receptor (GPCR) with weak homology to galanin receptors.²⁴ The human KP receptor (*KISS1R*) is also known as AXOR12, HH8, and hOT7T175, with the most common name being GPR54.²⁵ The way in which the KPs interact with the receptor has been reviewed by Trevisan et al.¹⁴

1.3 | Role of KP in reproduction

Fertility and reproductive function are regulated via the hypothalamic–pituitary–gonadal axis (HPG). This is a complex neurohormonal system of control, driven by GnRH in the hypothalamus, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in the pituitary and then steroids in the gonads.

Although known in the 1970s that the initiation of mammalian sexual maturation requires the activation of the hypothalamic GnRH neurons,²⁶ the mechanism responsible for it remained unknown. The key role of KP in the stimulation of GnRH neurons and, consequently, in the initiation of sexual maturation has been demonstrated by scientists led by the De Roux group,²⁷ on what was then referred to as family-related idiopathic hypogonadotrophic hypogonadism (IHH). In the siblings of an examined child, four out of five brothers developed symptoms of IHH (characterized as undeveloped testes, no pubic hair, and a 15-year-old skeletal system), and one of two sisters showed symptoms of partial hypogonadism (her breasts developed only partially and up to the age of 16 had only had one menstrual period). Each of his siblings had low blood levels of gonadotropins and gonadal hormones, and further tests showed that the family had a *KISS1R* gene variant. Based on these studies it was concluded that the *KISS1/KISS1R* system is responsible for initiating sexual maturation. Further, the research of Seminara et al,⁸ who diagnosed the syndrome of IHH in six members (four men and two women) of a family, showed it was due to a *KISS1* gene variant. The importance of the *KISS/KISS1R* system in the proper functioning of the HPG axis was also confirmed by later work of this group on mice with a *Kiss1r* gene variant. Thus, KP is essential in the initiation of puberty. *KISS1R* activates phospholipase C (PLC) when it is coupled to the G protein subunit, G_{q/11}α.¹⁴ PLC activation causes phosphatidylinositol bisphosphate to be hydrolyzed and form diacylglycerol (DAG).²⁸ DAG activates protein kinase C, which phosphorylates mitogen-activated protein kinases that then serve as activators for β-arrestin and inositol-1,4,5-triphosphate.²⁹ As a result of these cascades, calcium is released intracellularly to depolarize the neuron.³⁰ Calcium levels may increase intracellularly as a result of PLC-independent mechanisms, leading to opening

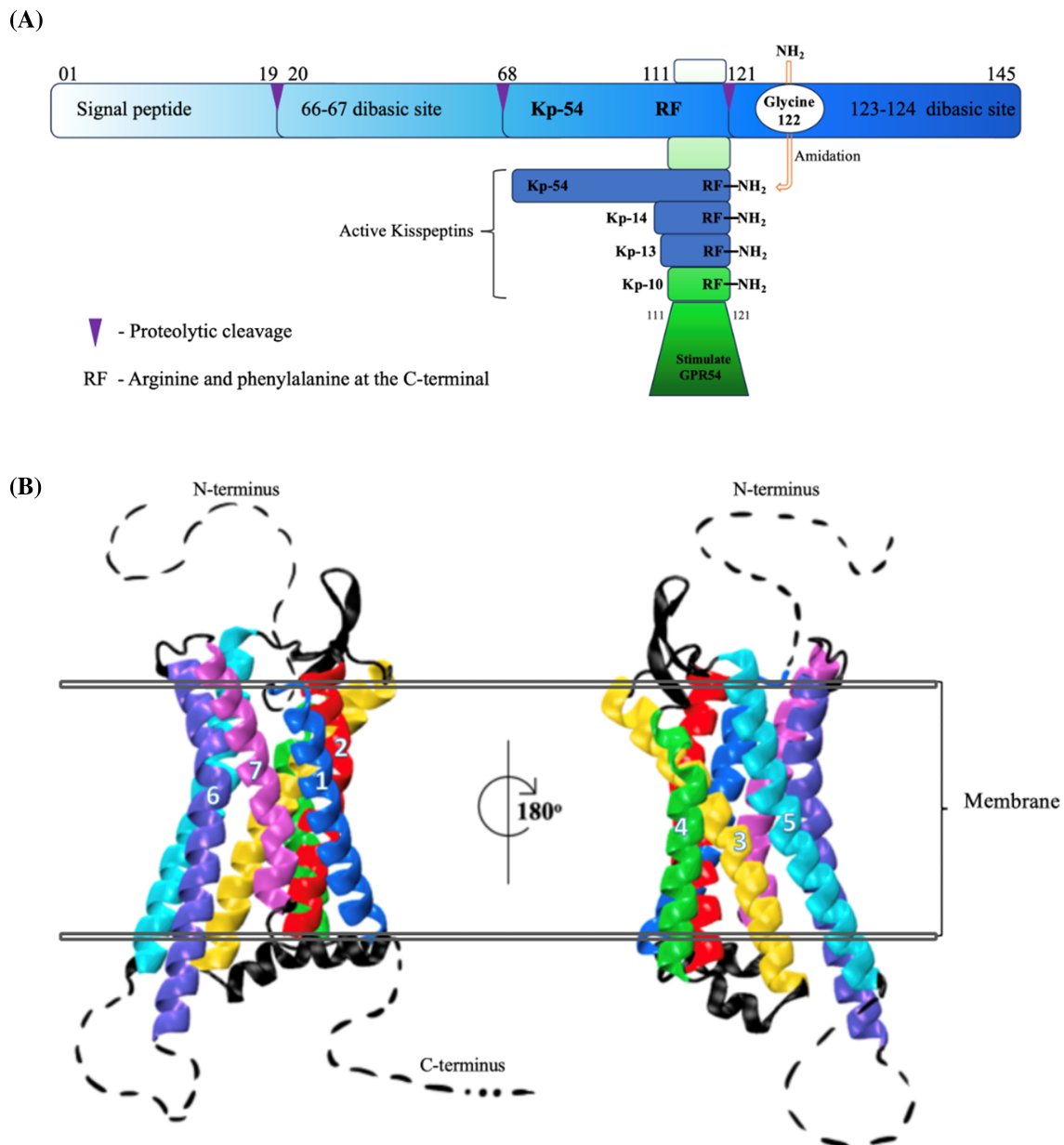
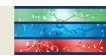


FIGURE 1 Kisspeptin and the human GPR54 structure. (A) Schematic diagram showing pre-pro-kisspeptin and the proteolytic cleavage pathway from which active kisspeptins Kp-10, Kp-13, Kp-14, and Kp-54 occur. (B) The 3-dimensional Cryo-EM structure of GPR54 (SWISS-MODEL, SMLT ID: 7xjk.1).¹² The membrane bilayer is indicated by the black double lines and the transmembrane helices of GPR54 and colored and numbered (Helix1: blue, Helix2: red, Helix3: yellow, Helix4: green, Helix5: cyan, Helix6: purple, and Helix7: pink), whereas the extra- and intracellular loops are depicted with black color. The dashed lines indicate the missing segments of the GPR54 reported crystal structure. Image was made using the VMD software.¹³ GPR54, G-protein-coupled receptor; KP, kisspeptin.

potassium channels and nonselective cation channels.³¹ Synapses are formed between KP and GnRH expressing neurons and KP neurons are depolarized, as are GnRH neurons. This depolarization causes release of LH and FSH.^{32,33} Prolonged exposure to KP desensitizes KISS1R.³² KP administration stimulates gonadotropin secretion in a wide range of species including rodents, goats, sheep, pigs, cows, horses, and monkeys³⁴ as well as humans.^{35–37}

In the peripheral reproductive system there is evidence that KP and KISS1R play a role in local control of reproductive function within the ovary, testis, uterus, and placenta.³⁸ Furthermore, KP is involved in all stages of reproduction including onset of puberty, menstrual cycle, pregnancy and in the menopause.^{14,39} The response of KP in both genders is different and the roles of KP and GnRH are reviewed comprehensively by Marquez et al.⁴⁰



1.4 | KP does not act alone

Within the hypothalamic arcuate nucleus (ARC), KP acts together with two cotransmitters: neurokinin B (NKB) and dynorphin (Dyn). The neurons responsible in the ARC are called KNDy (from the first letter of peptides: K – kisspeptin, N – neurokinin B, D – dynorphin).⁴¹ In rodents, NKB is a tachykinin peptide that binds to the NK3R.⁴² TAC3 is the name for NKB in humans, which acts on TAC3R.^{43,44} Dyn belongs to a class of endogenous opioid peptides that act on opioid kappa receptors.⁴⁵ In the hypothalamus, KP release is stimulated by NKB and inhibited by Dyn.⁴⁶ However, there are species differences in the colocalization of the aforementioned peptides, and a low degree of overlap between KP, NKB, and Dyn immunoreactivities found in the infundibular recess (equivalent to the ARC) of young men challenges KNDy neuron concepts in humans.⁴⁷ For further information, refer to the comprehensive review of the KNDy hypothesis by Lehman et al.⁴⁸ In mammals, besides the population of KP neurons in the ARC there is another population of KP-synthesizing neurons in the anterior preoptic area. In rodents, KP neurons are located in two main populations of the rostral periventricular area of the third ventricle (RP3V) and in the ARC.⁴⁸ In humans, both KP cell populations are also present, with the majority of neurons localized in the infundibular nucleus.^{49,50} Preovulatory surge of GnRH and LH are controlled by the first group of cells, and pulsatile LH release is governed by the second one that projects onto GnRH. Estradiol (E₂) works in the opposite manner on both populations of KP neurons. Whereas in the RP3V, KP synthesis⁵¹ is enhanced by E₂, in the ARC, estradiol inhibits the synthesis of KP. Our understanding of the KNDy neuronal network is critical to identifying new roles for KP, not only in reproduction.

1.5 | KP as a neuropeptide linking metabolism and reproduction and possible tool to treat both metabolic and reproduction dysfunction

Although KP control of reproduction is very well established, its involvement in metabolism regulations is still emerging. However, there are also interconnections between these two processes.

First, reproduction, which is necessary for the perpetuation of the species, is very costly in terms of energy consumption. Maturation and function of the HPG axis are tightly connected with the energy status of an individual.⁵² Historically, in paleolithic ages, symbols of fertility were presented as overweight women. Much later, in the

1960s and 1970s, the critical fat mass hypothesis was formulated that stated a need for a certain threshold of body fat mass to be reached in order for the attainment of menarche and for maintaining reproductive function later in life.⁵³

However, today there is a worldwide epidemic of obesity, and positive energy balance (especially excessive consumption of foods, high in sugars and fats), reduced physical activity, sedentary lifestyle, and limited physical activity are factors contributing to the development of this metabolic condition.⁵⁴ Moreover, this type of lifestyle promotes development of type 2 diabetes (T2D), which accounts for 90% of diabetes cases. In these patients besides metabolic problems, there are multiple secondary physiological alterations including disruptions of the menstrual cycle, premature childbirth, miscarriages, decrease in testosterone concentrations in men, and fertility impairment in both sexes.^{55,56} In men, obesity is also associated with impaired gonadal function and hypogonadism.⁵⁷ It has been hypothesized that testosterone (T) deficiency reported in obese and T2D patients is connected with decreased endogenous KP secretion and alterations in metabolic and endocrine factors.⁵⁸

In women with polycystic ovary syndrome (PCOS), obesity is common. It is pertinent to note that in Eastern Europe and America, about 50% of women are overweight.^{56,59–62} KP levels are reportedly higher in women with PCOS, and an overactive KISS system enhances HPG-axis activity. This in turn results in irregular menstrual cycles and excessive androgen release in these women (reviewed in⁶³). Moreover, fertility can be affected by factors such as body weight (BW) and composition, physical activity, and nutrient intake.⁶⁴ Impairment of the HPG axis, oocyte quality, and uterine receptivity have been reported in overweight and obese women.^{65,66} On the other hand, obese men show a total sperm count lower than normal weight controls.⁶⁷ Evidence suggests that physical activity and a proper diet could significantly improve reproductive outcomes.⁶⁴ Additionally, clinical data identify that a KP agonist, MVT-602, could be a potential drug for treatment of female reproductive disorders.⁶⁸ KP-10 administration stimulates serum T and LH secretion in men with T2D and mild hypogonadism.⁶⁹ Thus, the data support links between metabolism and reproduction and the role of KP in treatment of these conditions.

The World Health Organization provides the following definitions of being overweight and obese as abnormal or excessive fat accumulation that is a risk to health. Moreover, a body mass index (BMI) >25 kg/m² is categorized as overweight, and >30 as obese.⁷⁰ However, scientific findings indicate that the interplay between reproduction and metabolism occurs within the CNS, in



particular in the ARC. Here, several populations of neurons control food intake and metabolism such as neuropeptide Y (NPY), proopiomelanocortin (POMC), cocaine and amphetamine-regulated transcript, and a population express agouti-related peptide.^{71,72} Besides these peptides, there is strong evidence that KP neurons in the ARC play a role in conveying information on metabolism to GnRH neurons being a part of the HPG axis.^{52,73} Murine dual immunofluorescence studies have revealed close appositions between KP fibers and GnRH cell bodies, which increase in number throughout pubertal development.⁷⁴ Recent research has focused on afferent inputs to KP neurons especially in the area of energy balance, where under- or severe overnutrition suppresses fertility. It is suggested that KPs induce their metabolic effects indirectly via gonadal hormones and/or directly via the KP receptors in the brain, brown adipose tissue (BAT), and pancreas.³ Other evidence for the role of the KP system in metabolic functions comes from *Kiss1r*-knockout (KO) mice, which exhibit increased adiposity and reduced energy expenditure.

Finally, recent studies indicate a role of KP signaling on sexual behavior⁷⁵ (eg, sexual motivation, copulatory behavior, bonding⁷⁶). The role of hypothalamic KP in metabolism has also been confirmed in numerous animal studies in conditions such as undernutrition, obesity and diabetes, which are discussed subsequently. Additionally, the peripheral role of KP in the control of metabolism, primarily obesity and diabetes, is described next.⁷⁷

1.6 | What we can learn from animal models of obesity and diabetes about the role of KP in control of metabolism and reproduction and how we can translate this knowledge into the clinic

Many obesity experimental models exist, for example, genetically induced obesity, obesity caused by a high-fat (HFD), high-carbohydrate diets, or a combination of both.⁷⁸ Moreover, various animal fetal models of obesity and diabetes exist (reviewed in⁷⁹). The latter are based on the concept of fetal/early programming, according to which early environmental factors can permanently organize or imprint physiological and behavioral systems. Thus, according to these concepts environmental factor(s) such as maternal diet (eg, undernutrition or overnutrition) affect the structure and functions of tissues and organs. This in turn is in agreement with the developmental origins of health and disease approach, leading to lifelong effects, including development of metabolic and reproductive problems in offspring.⁸⁰

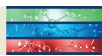
Similar to humans, in animal models of obesity, various dysfunctions are observed including raised body fat and triglyceride levels, glucose intolerance, and insulin resistance, which may lead (especially in extended exposure to HFD) to the development of T2D. A commonly used method to induce T2D in animals employs combination of feeding with HFD followed by injections of low doses of streptozotocin (a toxin that destroys the pancreas).⁸¹ Such animal models mimic the human condition, where T2D is often associated with obesity and a HFD.

Importantly, animal models mimic human findings with regard to reproductive problems reported in the case of obesity; for example, in obese women as well as monkeys and rodents fed with HFD, advanced puberty is observed.^{82–84} In search of possible mechanisms responsible for reproductive alterations in times of metabolic imbalance, a role of altered KP signaling, linking metabolism with reproduction is explored. Next we review data on central and peripheral roles of KP in regulation of metabolism and reproduction in animal models of obesity and diabetes. Numerous studies have revealed that in reproductive diseases (eg, hypogonadotropic hypogonadism and PCOS) and metabolic ones (eg, obesity, diabetes, undernutrition) there are alterations in the expression of KP in the hypothalamus.

1.7 | Alterations in hypothalamic KP expression

Hypothalamic *KISS1* directly stimulates GnRH neurons, which express *KISS1R*, and it was identified that patients with IHH (characterized by impaired secretion of gonadotropins FSH and LH) had inactivating polymorphisms in *KISS1R*. These findings were replicated in mice with *Kiss1* and *Kiss1R* variants.⁸

Moreover, in a mouse model of PCOS, characterized by hyperandrogenemia, chronic anovulation, cystic ovarian follicles, and LH and hyperpulsatility, changes in KP were reported. These animals showed marked elevated *Kiss1* expression and increased *Kiss1* neuronal activation in the ARC.⁸⁵ In prenatally androgenized (PNA) models of PCOS in female rats, a significant increase in the number of KP-immunopositive neurons in the ACR was found compared to control females.⁸⁶ Another PNA rat study reported increased *Kiss1* mRNA expression in the ARC.⁸⁷ Besides alterations in expression of *KISS1* in the reproductive disorders there are also convincing results on changes in this system in animal models of metabolic disorders. Quennell et al⁷³ showed that leptin deficiency and diet-induced obesity in mice were associated with reduced *Kiss1* expression in the hypothalamus.



This correlates with the concept that a decreased energy status negatively has an effect on fertility. Thus, a reduction in leptin (a hormone controlling food intake) also has a negative effect on fertility. Furthermore, increased leptin levels increase *Kiss1* gene expression. Fu and van den Pol (2010)⁷⁴ showed that *Kiss1* directly interacts with anorexigenic POMC neurons in the ARC through *Kiss1r* on the neurons. In addition, they demonstrated that *Kiss1* inhibits NPY neurons in the ARC, indicating that *Kiss1* may modulate appetite and energy homeostasis.

1.8 | Evidence from genetically modified animals

Furthermore, using *Kiss1r* KO mice Tolson et al⁸⁸ demonstrated that they were characterized by sex-specific differences in metabolic parameters. Whereas KO female mice showed an obese and diabetic phenotype, with increased BW, leptin levels, adiposity, and impaired glucose intolerance, male KO mice had a normal BW and glucose regulation.⁶⁰ However, the reason for these different phenotypes remains unknown. De Bond et al⁸⁹ subsequently found that despite this development, hypothalamic metabolic gene expression involved in the appetite regulating, including neuropeptide Y (*Npy*), proopiomelanocortin (*Pomc*), leptin receptor (*Lepr*), ghrelin receptor (*Ghsr*), and melanocortin receptors 3 and 4 (*Mc3r*, *Mc4r*) remained unaltered. Thus, these changes may be affected by peripheral rather than central influences. In follow-up developmental studies, Tolson et al⁹⁰ proved that at 6 weeks old (young adult), KO females already show altered adiposity, leptin levels, metabolism, and energy expenditure, despite reported normal BWs.

Sex differences in several metabolic parameters were also reported in mice lacking KP signaling due to global inactivation of *Kiss1r* also referred to as *Gpr54* in some literature⁹¹ (eg, displaying profound hypogonadism; *Gpr54*^{-/-}). These animals were compared to *Gpr54* null mice with selective reintroduction of *Gpr54* expression only in GnRH cells (*Gpr54*^{-/-}Tg) and preserved gonadal function. Velasco et al⁹² found that in male mice, global elimination of KP signaling manifested itself as decreased BW, suppression of feeding, and increased adiposity, without changes in glucose tolerance. On the other hand, *Gpr54*^{-/-} female mice had increased BW gain and adiposity and perturbed glucose tolerance, despite reduced food intake. *Gpr54*^{-/-}Tg rescued mice were characterized by altered BW gain in males and mild altered glucose tolerance in females. When animals were challenged and exposed to HFD, exaggerated BW gain and adiposity in global *Gpr54*^{-/-} mice of both sexes were observed,

with worse glucose tolerance, especially in females. In the case of the rescued *Gpr54*^{-/-}Tg males, intermediate BW gain and feeding profiles and impaired glucose tolerance were reported. On the other hand, rescued *Gpr54*^{-/-}Tg females were similar to controls in many parameters, except for a modest disruption of glucose tolerance following ovariectomy. Based on this study, a global role of KP signaling in the control of BW and metabolic homeostasis was concluded. Moreover, sexually dimorphic effects of KP in the regulation of BW gain, feeding, and responses to HFD were proved. Finally, in animal models of fasting, reduced *Kiss1* mRNA expression in the hypothalamus in rodents were reported.^{93,94} Short-term undernutrition in male and female prepubertal rats showed reduced whole hypothalamic *Kiss1* mRNA and increased hypothalamic *Kiss1r* mRNA compared with controls.⁹³

1.9 | Changes in peripheral KP expression

There is also evidence of the role of KP besides the brain in regulation of metabolism. *KISS1* and its receptor are expressed in peripheral tissues involved in the control of metabolism such as the pancreas, liver, and fat.⁵⁶ Next we discuss the role of KP in different metabolic organs. Importantly, as KP levels dramatically increase during pregnancy, we also present data linking alterations in this peptide with gestational diabetes.⁹⁵

1.9.1 | KP action in the pancreas

In the pancreas, the 54 amino acid KP isoform, Kp-54, increases glucose-induced insulin secretion from human and mouse islets, without changing basal secretion.^{46,96} Additionally, studies in rats have also found that an intracerebroventricular injection of the peptide had no effect on insulin levels, which confirms a peripheral site of action of Kp-54.⁹⁷ Moreover, it was revealed that Kp-10 and Kp-13 act directly on β -cells to potentiate insulin secretion stimulated by glucose in murine, porcine, and human islets.^{97,98} Finally, the expression of *KISS1* and *KISS1R* in the pancreas (mRNA and peptide) is altered by an HFD and T2D.⁹⁹

1.9.2 | KP action in the liver

In the liver, KP-10 administered peripherally had antioxidant and thus protective effects on liver metabolism.^{18,46,100,101} In diabetic mice (HFD-induced diabetes



and genetic leptin receptor-deficient db/db animals) liver KP levels were increased.¹⁸ Additionally, obese male rats fed a HFD and those with T2D also had increased liver KP expression.⁹⁹ Importantly, studies in patients with T2D revealed increased liver and plasma KP levels. The role of KP in the regulation of metabolism was also revealed in genetically modified animals. In a selective liver KP knockdown mouse model, depressed glucose-sensitive insulin secretion and improved glucose tolerance were found. Moreover, mice lacking liver *Kiss1r* when fed a HFD had improved glucose tolerance.¹⁸

In nonalcoholic fatty liver disease, that correlates with a rise in obesity and T2D, activation of the *Kiss1r* signaling pathway had therapeutic effects in HFD-fed C57BL/6J mice. Whereas in these animals, a deletion of hepatic *Kiss1r* exacerbated hepatic steatosis, whereas stimulation of *Kiss1r* offered protection against steatosis and decreased fibrosis.¹⁰²

1.9.3 | KP regulation of the adipose tissue

Kiss1 mRNA has been found in adipose tissue in rats⁹⁹ and humans.¹⁰³ Fasting has been shown to increase expression of *Kiss1* mRNA in rats, and an HFD decreases it. In women, there is a positive correlation between BMI and *KISS1* mRNA levels in omental (surrounding peritoneal organs) adipose tissue but not in subcutaneous fat.¹⁰³ In vitro studies on mouse 3 T3-L1 cells and isolated rat adipocytes have revealed expression of *Kiss1* and *Kiss1r* (mRNA and peptide) and explored a possible role of KP on lipid metabolism.¹⁰⁴ It was found that KP inhibited proliferation, viability, and adipogenesis in 3 T3-L1 cells and decreased expression of peroxisome proliferator-activated receptor- γ and CCAAT/enhancer-binding protein beta genes, factors that are involved in the differentiation processes and adipogenesis. Kp-10 also stimulated lipolysis in 3 T3-L1 cells and rat adipocytes by increasing expression of perilipin and hormone-sensitive lipase, as well as modulated glucose uptake and lipogenesis. Additionally, KP decreased glucose uptake and secretion of adiponectin and stimulated secretion of leptin from rat adipocytes.¹⁰⁴ From these in vitro studies, it was concluded that Kp-10 may decrease lipogenesis and slightly increase lipolysis. However, there is a need to perform more in vivo experiments on the role of KP on adipose tissue. It was already found that in underfed and fasting male rhesus monkeys there is a stimulatory effect of Kp-10 on adiponectin but not leptin levels.¹⁰⁵

As *Kiss1r* is expressed in BAT, KO studies by Tolson et al¹⁰⁶ explored the role of this expression in relation to obesity. The researchers first showed that global *Kiss1r*

KO mice have alterations in body temperature and BAT thermogenic gene expression, factors which could contribute to an obese phenotype. Later using Cre/lox technology they generated conditional *Kiss1r* KO exclusively in BAT (BAT-*Kiss1r* KO). These mice were not hypogonadal, but both sexes had lower BW and adiposity than controls. However, this phenotype was greater in females. Thus, it was confirmed that the previously observed obesity and decreased metabolism in global *Kiss1r* KOs reflect impaired KP signaling in non-BAT tissues. This study also added a role for endogenous KP signaling in BAT in modulating metabolism and thermogenesis. However, these experiments were performed on mice and further experiments are needed in different species.

1.9.4 | Trihormonal regulatory circuit linking role of KP in regulation of metabolism

Song et al¹⁸ proposed a trihormonal regulatory circuit between pancreatic α -cells (secreting glucagon), hepatocytes, and β cells (secreting insulin), identifying a crucial role for KP. According to this hypothesis, liver glucagon receptor activation stimulates insulin secretion by increased hepatic glucose production and hyperglycemia, and liver glucagon action may inhibit insulin secretion by stimulating KP production. Thus, in T2D patients, β cells are exposed to two counteracting stimuli, glucagon-induced hepatic glucose production, and hyperglycemia stimulation, whereas KP production inhibits glucose-stimulated insulin secretion. These findings suggest potential for KP antagonism as a therapeutic tool to improve β -cell function in diabetic patients.¹⁸ Indeed, it was found that KP-10 administered to men with T2D and central hypogonadism enabled increased T secretion.⁶⁹

1.10 | KP alterations both in metabolic and reproductive functions

Jayasena et al observed a massive placenta release of KP into the maternal circulation, suggesting a role for this peptide in pregnancy.⁹⁵ Due to the dramatic rise of circulating levels of KP during healthy pregnancy, it has been proposed as a potential biomarker of placental function. Furthermore, alterations in levels of this peptide are often connected with an increased risk of maternal and fetal complications.¹⁰⁷ It was also revealed that KP is a placental signal that plays a role in islet adaptation to pregnancy, maintaining maternal glucose homeostasis, acting through the β -cell *Kiss1r*. Consequently, it was found that decreased placental KP production and impaired KP-dependent β -cell compensation may play an



important role in the development of gestational diabetes in humans.¹⁰⁸

The KP system was also reported to be altered in reproductive organs such as ovaries and testes in animal models of obesity. An HFD administered to female rats at postweaning resulted in a marked suppression of ovarian *Kiss1* mRNA levels. Moreover, in the HFD group, the immunoreactivity of KP was significantly lower in theca cells from antral and preovulatory follicles.¹⁰⁹ KP and Kiss1r protein expression were reduced in testicular tissues in the diet-induced obese male mice.¹¹⁰

Recently, a role of KP was also expanded on behaviors such as olfactory-mediated partner preference, sexual motivation, copulatory behavior, bonding, mood, and emotions.⁷⁶ Thus, it would be of interest to study such behaviors in relation to KP in obese and diabetic animals.

In summary, in addition to the central role of KP in the hypothalamus in the regulation reproduction, there are convincing data about the role of this peptide in the regulation of metabolism.

1.11 | Clinical applications of KP

Reproductive dysfunction and metabolic disturbances are often seen together in conditions such as diabetes, obesity, eating disorders, and PCOS. KP may link reproduction and metabolism by obtaining signals about energy needs at differing stages of development and influencing HPG responses. For example, leptin may regulate metabolic signals on KP as in the ARC, 40% of KP neurons express leptin receptors, whereas GnRH neurons do not.¹¹¹ Although early studies showed direct linkage between KP and leptin, GnRH and leptin connections are more complex and may include a range of other molecules such as ghrelin, NPY, and POMC, as well as involving estradiol, testosterone, progesterone, and stress hormones.⁴⁰ By studying the role of KP in disorders involving reproductive and/or metabolic disturbances, our knowledge of the biology of KP is expanding.

Advances in the field of KP research are represented by a number of clinical trials, which have increased in the last decade. Table 1 shows recent and ongoing KP clinical trials and their status. The main studies are being carried out on kisspeptin 112–121 (or Kp-10) likely because Kp-10 is the smallest length needed to stimulate the receptor.¹⁴ Table 1 summarizes the range of studies that are being conceptualized and the countries that are interested in this field. From this perspective, the focus of the majority of the studies is on fertility issues, or rather conditions associated with infertility (such as PCOS), improving implantation and successful pregnancy. This

then correlates to where funding is obtained from to carry out these studies. Furthermore, this table highlights that, to date, there are few published clinical studies on both fertility and metabolism. This suggests that the connectivity between fertility and metabolism is still in its infancy, but it is envisaged that this will change in the future.¹¹⁹ As peripherally administered kisspeptin-54 has been demonstrated to cross the blood–brain barrier¹²⁰ and potentially affect regulation of food intake. Thus, further studies examining the acute and chronic effects of KP on food intake in obese and diabetic patients are needed. It was already found that KP administration to healthy men enhances insulin secretion in response to an intravenous glucose load, without influence on fasting insulin levels or insulin levels in response to delivery of food ad libitum.¹¹⁹ This may also open a possibility for a potential therapeutic role for KP treatment in a state of hyperglycemia observed during pregnancy.^{121,122} Finally, it was already proved that KP could be used to enhance both reproductive hormones and insulin levels in obese hypogonadal men with T2D. However, further studies including those that use imaging techniques are needed to explore the role of KP in regulation of metabolism. Such experiments have just begun to emerge. In a study using functional magnetic resonance imaging it was recently found that peripheral administration of KP to healthy men does not alter brain responses to visual food stimuli¹²³ or psychometric indices of appetite. However, this study was performed only on men and as was previously discussed, the KP system is sexually dimorphic. Moreover, the odors cue was not taken into account. Finally, in view of their presented findings it would be of interest to study KP effects in obese and T2D patients of different genders.

2 | CONCLUDING REMARKS

Emerging data from experiments conducted on animals as well as from human clinical trials relating to KP indicate a valuable therapeutic target to treat both metabolic and reproductive dysfunctions. However, it is important to consider differences in gender outcomes related to the KP system. Thus, more research is needed to elucidate the mechanisms of action to develop appropriate therapeutics. There is also recent evidence that KP is involved in emotional behavior including fear, mood, and social and sexual behavior (sexual motivation, copulatory behavior, bonding⁷⁶) that makes sense to enable successful reproduction but may also serve to help control eating disorders and depression.¹²⁴ This is an exciting field, which has yet to reveal its full therapeutic potential.



TABLE 1 Recent clinical trials involving KP.

| Study and phase | Status | Conditions | Interventions | Results | ClinicalTrials.gov identifier (location) |
|---|----------------------------|--|--------------------------------|---------|--|
| Metabolism studies | | | | | |
| Evaluation of kisspeptin glucose-stimulated insulin secretion with oral glucose tolerance Test (Phase I) | R ~ 2024 (n = 16) | • Metabolic diseases | Kisspeptin | N/A | NCT04958109 (United States) |
| Evaluation of kisspeptin stimulated insulin with hyperglycemic clamp (Phase I) | R ~ 2024 (n = 12) | • Metabolic disease | KP-10 | N/A | NCT05456854 (United States) |
| Evaluation of kisspeptin glucose-stimulated insulin secretion with physiologic mixed meal tolerance (Phase I) | R ~ 2023 (n = 25) | • Assessment of beta-cell responsiveness in healthy women | Kp-10 | N/A | NCT04532801 (United States) |
| KP-10 and insulin secretion in men (Phase III) | C 2014 (n = 14) | • Action on healthy and obese diabetic men | KP-10 | No | NCT03771326 (Pakistan) |
| Fertility studies | | | | | |
| Detection of kisspeptins and miRNAs in patients with nonviable pregnancy (N/A) | R Prospective (n = 433) | • Nonviable pregnancy | N/A – diagnostic observational | N/A | NCT03877939 (Spain) |
| Reproductive hormones during sustained administration of kisspeptin (N/A) | R ~ 2027 (n = 76) | • Fertility disorders • Hypothalamic dysfunction | Kisspeptin | N/A | NCT081924 (United Kingdom) |
| Opioid Antagonism in Individuals Ascertained Through the Partners Health Care Biobank (Phase I) | R ~ 2025 (n = 23) | • Reproductive disorders | Kisspeptin 112–121 | N/A | NCT04975347 (United States) |
| Administration of kisspeptin to subjects with reproductive disorders (Phase I) | R ~ 2025 (n = 496) | • Hypogonadotropic Hypogonadism • Kallmann syndrome • GnRH deficiency • Polycystic Ovarian syndrome • Hyperprolactinemia | Kisspeptin 112–121 | N/A | NCT00914823 (United States) |
| Neuropeptides in human reproduction (Phase I) | R ~ 2025 (n = 128) | • Hypogonadotropic Hypogonadism | Kisspeptin 112–121 | N/A | NCT01952782 (United States) |
| Prolonged pulsatile kisspeptin administration in hypogonadotropic hypogonadism | R ~ 2025 (n = 24) | • Hypogonadotropic Hypogonadism | Kisspeptin 112–121 | N/A | NCT04648969 (United States) |
| Opioid antagonism in hypergonadotropic hypogonadism (Phase II) | R ~ 2024 (n = 23) | • Hypogonadotropic Hypogonadism | Kisspeptin | N/A | NCT04975334 (United States) |
| Kisspeptin administration subcutaneously to patients with reproductive disorders (KASPR) (Phase I) | R ~ 2024 (n = 50) | • Hypogonadotropic Hypogonadism • Hypothalamic Amenorrhea | Kisspeptin 112–121 | N/A | NCT05633966 (United States) |
| Administration of kisspeptin in patients with hyperprolactinemia (Phase II) | R ~ 2023 (n = 60) | • Hyperprolactinemia • Hypogonadism | Kisspeptin 112–121 | N/A | NCT02956447 (United States) |

(Continues)



TABLE 1 (Continued)

| Study and phase | Status | Conditions | Interventions | Results | ClinicalTrials.gov identifier (location) |
|--|---|---|---|---|--|
| Kisspeptin in the evaluation of delayed puberty (Phase I) | R ~ 2023 (<i>n</i> = 60) | <ul style="list-style-type: none"> Delayed Puberty Kallmann Syndrome Hypogonadotropic Hypogonadism GnRH deficiency | Kisspeptin 112–121 | N/A | NCT01438034 (United States) |
| Elucidating kisspeptin physiology by blocking kisspeptin signaling (Phase I) | C 2016 (<i>n</i> = 96) | <ul style="list-style-type: none"> Hypogonadotropic Hypogonadism Healthy postmenopausal women Primary gonadal insufficiency in men | Kisspeptin 112–121 | Yes ³⁵ | NCT01438073 (United States) |
| Age-dependent changes in the responsiveness of hypothalamic pituitary gonadal axis in men | C 2015 (<i>n</i> = 15) | <ul style="list-style-type: none"> Sterility Reproductive physiological phenomena | Kp-10 | Yes ¹¹² | NCT03315325 (Pakistan) |
| Link between the sensitivity of kisspeptin signaling and pubertal onset in boys (Phase III) | C 2015 (<i>n</i> = 30) | <ul style="list-style-type: none"> Reproductive physiological phenomena | Kp-10 | Yes ¹¹³ | NCT03286517 (Pakistan) |
| Effects of TAK-448 in middle-aged and older men with low testosterone (Phase II) | T 2016 (<i>n</i> = 17, intended <i>n</i> = 99) | <ul style="list-style-type: none"> Low testosterone | TAK-448 (KISS1R agonist, kisspeptin analog) | Partially as terminated early so not analyzed but available in database | NCT02381288 (United States) |
| A Phase 2a pharmacodynamic study of TAK-448 in participants with hypogonadotropic hypogonadism (Phase IIa) | T 2015 (<i>n</i> = 15, intended <i>n</i> = 48) | <ul style="list-style-type: none"> Hypogonadotropic Hypogonadism | TAK-448 (KISS1R agonist, kisspeptin analog) | Partially as terminated early. Published in ¹¹⁴ | NCT02369796 (United States) |
| Serum kisspeptin: A predictive marker for miscarriage or not (N/A) | C 2020 (<i>n</i> = 182) | <ul style="list-style-type: none"> Miscarriage | N/A – observational KP levels | No | NCT03940495 (China) |
| Tachykinin and Kisspeptin expression in human granulosa and cumulus cells (N/A) | C 2019 (<i>n</i> = 236) | <ul style="list-style-type: none"> Infertility | N/A – observational KISS1 and KISS1R levels | Yes ¹¹⁵ | NCT02877992 (Spain) |
| Kisspeptin/GPR54 pathway and early puberty (N/A) | C 2019 (<i>n</i> = 628) | <ul style="list-style-type: none"> Precocious puberty | N/A – observational KP levels | Yes ¹¹⁶ | Yes ¹¹⁶ |
| Kisspeptin levels in early pregnancy (N/A) | C 2019 (<i>n</i> = 88) | <ul style="list-style-type: none"> Early pregnancy Ectopic pregnancy | N/A – diagnostic observational | No | NCT04371991 (Turkey) |
| Serum kisspeptin levels in infertile women (N/A) | C 2017 (<i>n</i> = 90) | <ul style="list-style-type: none"> Infertility Polycystic ovary syndrome Male factor infertility | N/A – observational | Yes ¹¹⁷ | NCT03018314 (Turkey) |
| The use of the hormone kisspeptin in in vitro fertilization” treatment | C 2016 (<i>n</i> = 175) | <ul style="list-style-type: none"> Infertility | Kisspeptin, Kisspeptin-54 | Yes ¹¹⁸ | NCT01667406 (United Kingdom) |
| Metabolism and fertility studies | | | | | |
| Kisspeptin influence on glucose homeostasis (Phase I) | R ~ 2024 (<i>n</i> = 413) | <ul style="list-style-type: none"> Impaired glucose tolerance Hypogonadism | Kisspeptin 112–121 | N/A | NCT02953834 (United States) |

Abbreviations: C, Completed; GnRH, gonadotropin-releasing hormone; KP, kisspeptin; N/A, not applicable; R, recruiting; T, terminated.



FUNDING INFORMATION


Nicola Woods was sponsored through a Biotechnology and Biological Sciences Research Council (BBSRC) Case studentship: grant number BB/F017642/1. Abdullah Alzahrani was funded by the Royal Embassy of Saudi Arabi-Saudi Cultural Bureau in London. Elpiniki Paspali is sponsored through a University of Strathclyde studentship. Joanna Sliwowska is supported by the National Science Centre in Krakow, Poland (OPUS grant 2015/17/B/NZ4/02021) and the statutory funding (506-511-09-00) from the Faculty of Veterinary Medicine and Animal Science, Poznan University of Life Sciences, Poland to Joanna Sliwowska.

DISCLOSURE

No disclosures.

ORCID

Joanna Helena Sliwowska  <https://orcid.org/0000-0001-6981-9653>

Valerie Anne Ferro  <https://orcid.org/0000-0003-1967-3603>

REFERENCES

- Mead EJ, Maguire JJ, Kuc RE, Davenport AP. Kisspeptins: a multifunctional peptide system with a role in reproduction, cancer and the cardiovascular system. *Br J Pharmacol*. 2007; 151:1143-1153.
- Wolfe A, Hussain MA. The emerging role(s) for kisspeptin in metabolism in mammals. *Front Endocrinol (Lausanne)*. 2018; 9:1-10.
- Izzi-Engbeaya C, Dhillon WS. Emerging roles for kisspeptin in metabolism. *J Physiol*. 2022;600:1079-1088.
- Bhattacharya M, Babwah AV. Kisspeptin: beyond the brain. *Endocrinol (United States)*. 2015;156:1218-1227.
- Schally AV. Aspects of hypothalamic regulation of the pituitary gland. *Science (80)*. 1978;202:18-28.
- Aparicio SAJR. Kisspeptins and GPR54—the new biology of the mammalian GnRH axis. *Cell Metab*. 2005;1:293-296.
- Ohtaki T, Shintani Y, Honda S, et al. Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. *Nature*. 2001;411:613-617.
- Seminara SB, Messager S, Chatzidaki EE, et al. The GPR54 gene as a regulator of puberty. *Obstet Gynecol Surv*. 2004;59: 351-353.
- Cortés ME, Carrera B, Rioseco H, Pablo del Río J, Vigil P. The role of Kisspeptin in the onset of puberty and in the ovulatory mechanism: a mini-review. *J Pediatr Adolesc Gynecol*. 2015; 28:286-291.
- Lee JH, Miele ME, Hicks DJ, et al. KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. *J Natl Cancer Inst*. 1996;88:1731-1737.
- Popa SM, Clifton DK, Steiner RA. The role of kisspeptins and GPR54 in the neuroendocrine regulation of reproduction. *Annu Rev Physiol*. 2008;70:213-238.
- SWISS-MODEL: Q969F8 (KISSR_HUMAN) Homo sapiens (Human). KiSS-1 receptor. URL <https://swissmodel.expasy.org/repository/uniprot/Q969F8>
- Humphrey W, Dalke A, Schulten K. Sartorius products. *J Mol Graph*. 1996;14:33-38.
- Trevisan CM, Montagna E, de Oliveira R, et al. Kisspeptin/GPR54 system: what do we know about its role in human reproduction? *Cell Physiol Biochem*. 2018;49:1259-1276.
- De Pedro MA, Morán J, Díaz I, et al. Circadian Kisspeptin expression in human term placenta. *Placenta*. 2015;36:1337-1339.
- Wassie T, Liu G, Jiang X, et al. Immunization against Kisspeptin-54 perturb hypothalamic-pituitary-testicular signaling pathway in ram lambs. *Theriogenology*. 2019;125: 193-202.
- Hu KL, Zhao H, Chang HM, Yu Y, Qiao J. Kisspeptin/kisspeptin receptor system in the ovary. *Front Endocrinol (Lausanne)*. 2018;8:1-14.
- Song WJ, Mondal P, Wolfe A, et al. Glucagon regulates hepatic kisspeptin to impair insulin secretion. *Cell Metab*. 2014;19:667-681.
- Loosen SH, Luedde M, Lurje G, et al. Serum levels of Kisspeptin are elevated in patients with pancreatic cancer. *Dis Markers*. 2019;2019:1-15.
- Kauff AS, Smith JT. *Kisspeptin Signaling in Reproductive Biology*. Springer; 2013.
- Yeo SH, Colledge WH. The role of Kiss1 neurons as integrators of endocrine, metabolic, and environmental factors in the hypothalamic-pituitary-gonadal axis. *Front Endocrinol (Lausanne)*. 2018;9:1-13.
- Sivalingam M, Parhar IS. Hypothalamic kisspeptin and kisspeptin receptors: species variation in reproduction and reproductive behaviours. *Front Neuroendocrinol*. 2022;64:100951.
- Guzman S, Brackstone M, Radovick S, Babwah AV, Bhattacharya MM. KiSS1/KiSS1R in cancer: friend or foe? *Front Endocrinol (Lausanne)*. 2018;9:1-9.
- Lee DK, Nguyen T, O'Neill GP, et al. Discovery of a receptor related to the galanin receptors. *FEBS Lett*. 1999;446:103-107.
- Kotani M, Detheux M, Vandenbogaerde A, et al. The metastasis suppressor gene KiSS-1 encodes Kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. *J Biol Chem*. 2001;276:34631-34636.
- Burgus R, Butcher M, Amoss M, et al. Primary structure of the ovine hypothalamic luteinizing hormone-releasing factor (LRF). *Proc Natl Acad Sci U S A*. 1972;69:278-282.
- De Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. *Proc Natl Acad Sci U S A*. 2003;100:10972-10976.
- Franssen D, Tena-Sempere M. The kisspeptin receptor: a key G-protein-coupled receptor in the control of the reproductive axis. *Best Pract Res Clin Endocrinol Metab*. 2018;32:107-123.
- Ke R, Ma X, Lee LTO. Understanding the functions of kisspeptin and kisspeptin receptor (KiSS1R) from clinical case studies. *Peptides*. 2019;120:170019.
- Oakley AE, Clifton DK, Steiner RA. Kisspeptin signaling in the brain. *Endocr Rev*. 2009;30:713-743.
- Zhang C, Roepke TA, Kelly MJ, Rønnekleiv OK. Kisspeptin depolarizes gonadotropin-releasing hormone neurons through



- activation of TRPC-like cationic channels. *J Neurosci.* 2008;28:4423-4434.
32. Yang R, Wang YM, Zhang L, Zhao ZM, Zhao J, Peng SQ. Kisspeptin signalling and its roles in humans. *Singapore Med J.* 2015;56:649-656.
 33. Yang R, Wang YM, Zhang L, Zhao ZM, Zhao J, Peng SQ. Prepubertal exposure to an oestrogenic mycotoxin zearalenone induces central precocious puberty in immature female rats through the mechanism of premature activation of hypothalamic kisspeptin-GPR54 signaling. *Mol Cell Endocrinol.* 2016;437:62-74.
 34. Abbara A, Ratnasabapathy R, Jayasena CN, Dhillon WS. The effects of kisspeptin on gonadotropin release in non-human mammals. *Adv Exp Med Biol.* 2013;784:63-87.
 35. Lippincott MF, Chan YM, Morales DR, Seminara SB. Continuous kisspeptin administration in postmenopausal women: impact of estradiol on luteinizing hormone secretion. *J Clin Endocrinol Metab.* 2017;102:2091-2099.
 36. George JT, Anderson RA, Millar RP. Kisspeptin-10 stimulation of gonadotrophin secretion in women is modulated by sex steroid feedback. *Hum Reprod.* 2012;27:3552-3559.
 37. Skorupskaitė K, George JT, Veldhuis JD, Millar RP, Anderson RA. Kisspeptin and neurokinin B interactions in modulating gonadotropin secretion in women with polycystic ovary syndrome. *Hum Reprod.* 2020;35:1421-1431.
 38. Cao Y, Li Z, Jiang W, Ling Y, Kuang H. Reproductive functions of Kisspeptin/KISS1R Systems in the Periphery. *Reprod Biol Endocrinol.* 2019;17:1-9.
 39. Rance NE. Menopause and the human hypothalamus: evidence for the role of kisspeptin/neurokinin B neurons in the regulation of estrogen negative feedback. *Peptides.* 2009;30:111-122.
 40. Marques P, Skorupskaitė K, George JT, Anderson RA. Physiology of GnRH and Gonadotropin Secretion. 2000. <https://pubmed.ncbi.nlm.nih.gov/25905297/> accessed 12 Feb 2023.
 41. Lehman MN, Coolen LM, Goodman RL. Minireview: Kisspeptin/neurokinin B/dynorphin (KNDy) cells of the arcuate nucleus: a central node in the control of gonadotropin-releasing hormone secretion. *Endocrinology.* 2010;151:3479-3489.
 42. Lomniczi A, Wright H, Castellano JM, Sonmez K, Ojeda SR. A system biology approach to identify regulatory pathways underlying the neuroendocrine control of female puberty in rats and nonhuman primates. *Horm Behav.* 2013;64:175-186.
 43. Topaloglu AK, Reimann F, Guclu M, et al. TAC3 and TACR3 mutations in familial hypogonadotropic hypogonadism reveal a key role for neurokinin B in the central control of reproduction. *Nat Genet.* 2009;41:354-358.
 44. Liu Y, Wang Q, Wang X, et al. NKB/NK3 system negatively regulates the reproductive axis in sexually immature goldfish (*Carassius auratus*). *Gen Comp Endocrinol.* 2019;281:126-136.
 45. O'Connor C, White KL, Doncescu N, et al. NMR structure and dynamics of the agonist dynorphin peptide bound to the human kappa opioid receptor. *Proc Natl Acad Sci U S A.* 2015;112:11852-11857.
 46. Dudek M, Ziarniak K, Sliwowska JH. Kisspeptin and metabolism: the brain and beyond. *Front Endocrinol (Lausanne).* 2018;9:1-8.
 47. Hrabovszky E, Sipos MT, Molnár CS, et al. Low degree of overlap between kisspeptin, neurokinin B, and dynorphin immunoreactivities in the infundibular nucleus of young male human subjects challenges the KNDy neuron concept. *Endocrinology.* 2012;153:4978-4989.
 48. Lehman MN, He W, Coolen LM, Levine JE, Goodman RL. Does the kndy model for the control of gonadotropin-releasing hormone pulses apply to monkeys and humans? *Semin Reprod Med.* 2019;37:71-83.
 49. Hrabovszky E. Neuroanatomy of the human hypothalamic kisspeptin system. *Neuroendocrinology.* 2014;99:33-48.
 50. Rometo AM, Krajewski SJ, Lou VM, Rance NE. Hypertrophy and increased kisspeptin gene expression in the hypothalamic infundibular nucleus of postmenopausal women and ovariectomized monkeys. *J Clin Endocrinol Metab.* 2007;92:2744-2750.
 51. Adachi S, Yamada S, Takatsu Y, et al. Involvement of anteroventral periventricular metastin/kisspeptin neurons in estrogen positive feedback action on luteinizing hormone release in female rats. *J Reprod Dev.* 2007;53:367-378.
 52. Manfredi-Lozano M, Roa J, Tena-Sempere M. Connecting metabolism and gonadal function: novel central neuropeptide pathways involved in the metabolic control of puberty and fertility. *Front Neuroendocrinol.* 2018;48:37-49.
 53. Frisch RE, Revelle R. Height and weight at menarche and a hypothesis of critical body weights and adolescent events. *Obstet Gynecol Surv.* 1971;26:254-255.
 54. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol.* 2019;15:288-298.
 55. Mahutte N, Kamga-Ngande C, Sharma A, Sylvestre C. Obesity and reproduction. *J Obstet Gynaecol Can.* 2018;40:950-966.
 56. Pasquali R, Patton L, Gambineri A. Obesity and infertility. *Curr Opin Endocrinol Diabetes Obes.* 2007;14:482-487.
 57. Carrageta DF, Oliveira PF, Alves MG, Monteiro MP. Obesity and male hypogonadism: Tales of a vicious cycle. *Obes Rev.* 2019;20:1148-1158.
 58. George JT, Millar RP, Anderson RA. Hypothesis: kisspeptin mediates male hypogonadism in obesity and type 2 diabetes. *Neuroendocrinology.* 2010;91:302-307.
 59. Glass AR, Swerdloff RS, Bray GA, Dahms WT, Atkinson RL. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. *J Clin Endocrinol Metab.* 1977;45:1211-1219.
 60. Lake PC, Cole TJ. Women's reproductive health: the role of body mass index in early and adult life. *Int J Obes (Lond).* 1997;21:432-438.
 61. Gawalek M, Sliwowska JH. Neuronal basis of reproductive dysfunctions associated with diet and alcohol: from the womb to adulthood. *Reprod Biol.* 2015;15:69-78.
 62. Marija S, Dragan V, Svetlana R, Nela D. Socioeconomic inequalities in overweight and obesity in Serbia: data from 2013 national health survey. *Front Pharmacol.* 2018;8:1-7.
 63. Tang R, Ding X, Zhu J. Kisspeptin and polycystic ovary syndrome. *Front Endocrinol (Lausanne).* 2019;10:10.
 64. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. *Obstet Gynecol.* 2007;110:1050-1058.
 65. Bellver J, Ayllón Y, Ferrando M, et al. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. *Fertil Steril.* 2010;93:447-454.
 66. Klop B, Elte JWF, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients.* 2013;5:1218-1240.



67. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril*. 2010;93:2222-2231.
68. Abbara A, Eng PC, Phylactou M, et al. Kisspeptin receptor agonist has therapeutic potential for female reproductive disorders. *J Clin Invest*. 2020;130:6739-6753.
69. George JT, Veldhuis JD, Tena-Sempere M, Millar RP, Anderson RA. Exploring the pathophysiology of hypogonadism in men with type 2 diabetes: Kisspeptin-10 stimulates serum testosterone and LH secretion in men with type 2 diabetes and mild biochemical hypogonadism. *Clin Endocrinol (Oxf)*. 2013;79:100-104.
70. World Health Organization. Diabetes. 2021. Accessed February 11, 2023 <https://www.who.int/en/news-room/fact-sheets/detail/diabetes>
71. Hill JW, Elmquist JK, Elias CF. Hypothalamic pathways linking energy balance and reproduction. *Am J Physiol Endocrinol Metab*. 2008;294:827-832.
72. Myers MG, Olson DP. Central nervous system control of metabolism. *Nature*. 2012;491:357-363.
73. Bouret SG. Development of hypothalamic circuits that control food intake and energy balance. *Appetite and Food Intake*. CRC Press; 2017:135-154.
74. Clarkson J, Herbison AE. Postnatal development of kisspeptin neurons in mouse hypothalamus; sexual dimorphism and projections to gonadotropin-releasing hormone neurons. *Endocrinology*. 2006;147:5817-5825.
75. Harter CJL, Kavanagh GS, Smith JT. The role of kisspeptin neurons in reproduction and metabolism. *J Endocrinol*. 2018; 238:R173-R183.
76. Mills EG, Yang L, Abbara A, Dhillo WS, Comninou AN. Current perspectives on Kisspeptins role in behaviour. *Front Endocrinol (Lausanne)*. 2022;13:13. doi:10.3389/FENDO.2022.928143
77. World Health Organization. Global Report on Diabetes. 2016. Accessed February 11, 2023 <https://www.who.int/publications/i/item/9789241565257>
78. Fernandes MR, de Lima NV, Rezende KS, Santos ICM, Silva IS, Guimarães R d CA. Animal models of obesity in rodents. An integrative review. *Acta Cir Bras*. 2016;31:840-844.
79. Grzęda E, Matuszewska J, Ziarniak K, et al. Animal Foetal models of obesity and diabetes – from laboratory to clinical settings. *Front Endocrinol (Lausanne)*. 2022;13:1-24.
80. Barker D. The fetal and infant origins of adult disease the womb may be more important than the home. *BMJ*. 1990;301: 1111.
81. Lu G, Luo X, Liu Z, Yang L, Lin C, Xu M. Protective effect of vanillin in streptozotocin-induced diabetes in neonatal rats via attenuation of oxidative stress and inflammation. *Trop J Pharm Res*. 2019;18:349-355.
82. Terasawa E, Kurian JR, Keen KL, Shiel NA, Colman RJ, Capuano SV. Body weight impact on puberty: effects of high-calorie diet on puberty onset in female rhesus monkeys. *Endocrinology*. 2012;153:1696-1705.
83. Loredana Marcovecchio M, Chiarelli F. Obesity and growth during childhood and puberty. *World Rev Nutr Diet*. 2013;106: 135-141.
84. Sánchez-Garrido MA, Castellano JM, Ruiz-Pino F, et al. Metabolic programming of puberty: sexually dimorphic responses to early nutritional challenges. *Endocrinology*. 2013;154:3387-3400.
85. Esparza LA, Schafer D, Ho BS, Thackray VG, Kauffman AS. Hyperactive LH pulses and elevated Kisspeptin and NKB gene expression in the arcuate nucleus of a PCOS mouse model. *Endocrinol*. 2020;161:1-15.
86. Osuka S, Iwase A, Nakahara T, et al. Kisspeptin in the hypothalamus of 2 rat models of polycystic ovary syndrome. *Endocrinology*. 2017;158:367-377.
87. Yan X, Yuan C, Zhao N, Cui Y, Liu J. Prenatal androgen excess enhances stimulation of the GNRH pulse in pubertal female rats. *J Endocrinol*. 2014;222:73-85.
88. Tolson KP, Garcia C, Yen S, et al. Impaired kisspeptin signaling decreases metabolism and promotes glucose intolerance and obesity. *J Clin Invest*. 2014;124:3075-3079.
89. De Bond JAP, Tolson KP, Nasamran C, Kauffman AS, Smith JT. Unaltered hypothalamic metabolic gene expression in Kiss1r knockout mice despite obesity and reduced energy expenditure. *J Neuroendocrinol*. 2016;28:1-20.
90. Tolson KP, Garcia C, Delgado I, Marooki N, Kauffman AS. Metabolism and energy expenditure, but not feeding or glucose tolerance, are impaired in young kiss1r ko female mice. *Endocrinology*. 2016;157:4192-4199.
91. Kirby HR, Maguire JJ, Colledge WH, Davenport AP. International Union of Basic and Clinical Pharmacology. LXXVII. Kisspeptin receptor nomenclature, distribution, and function. *Pharmacol Rev*. 2010;62:565-578.
92. Velasco I, León S, Barroso A, et al. Gonadal hormone-dependent vs. -independent effects of kisspeptin signaling in the control of body weight and metabolic homeostasis. *Metabolism*. 2019;98:84-94.
93. Castellano JM, Navarro VM, Fernández-Fernández R, et al. Changes in hypothalamic KiSS-1 system and restoration of pubertal activation of the reproductive axis by kisspeptin in undernutrition. *Endocrinology*. 2005;146:3917-3925.
94. Luque RM, Kineman RD, Tena-Sempere M. Regulation of hypothalamic expression of KiSS-1 and GPR54 genes by metabolic factors: analyses using mouse models and a cell line. *Endocrinology*. 2007;148:4601-4611.
95. Jayasena CN, Comninou AN, Narayanaswamy S, et al. The identification of elevated urinary kisspeptin-immunoreactivity during pregnancy. *Ann Clin Biochem*. 2015;52:395-398.
96. Hauge-Evans AC, Richardson CC, Milne HM, Christie MR, Persaud SJ, Jones PM. A role for kisspeptin in islet function. *Diabetologia*. 2006;49:2131-2135.
97. Bowe JE, Foot VL, Amiel SA, et al. GPR54 peptide agonists stimulate insulin secretion from murine, porcine and human islets. *Islets*. 2012;4:20-23.
98. Schwetz TA, Reissaus CA, Piston DW. Differential stimulation of insulin secretion by glp-1 and kisspeptin-10. *PLoS One*. 2014;9:1-10.
99. Dudek M, Kołodziejki PA, Pruszyńska-Oszmałek E, et al. Effects of high-fat diet-induced obesity and diabetes on Kiss1 and GPR54 expression in the hypothalamic-pituitary-gonadal (HPG) axis and peripheral organs (fat, pancreas and liver) in male rats. *Neuropeptides*. 2016;56:41-49.



100. Aydin M, Oktar S, Yonden Z, Ozturk OH, Yilmaz B. Direct and indirect effects of kisspeptin on liver oxidant and antioxidant systems in young male rats. *Cell Biochem Funct.* 2010;28:293-299.
101. Hou Y, Wang X, Ping J, et al. Metabonomics approach to assessing the modulatory effects of Kisspeptin-10 on liver injury induced by heat stress in rats. *Sci Rep.* 2017;7:1-10.
102. Guzman S, Dragan M, Kwon H, et al. Targeting hepatic kisspeptin receptor ameliorates nonalcoholic fatty liver disease in a mouse model. *J Clin Invest.* 2022;132:e145889.
103. Cockwell H, Wilkinson DA, Bouzayen R, Imran SA, Brown R, Wilkinson M. KISS1 expression in human female adipose tissue. *Arch Gynecol Obstet.* 2013;287:143-147.
104. Pruszyńska-Oszmałek E, Kołodziejcki PA, Sassek M, Sliwowska JH. Kisspeptin-10 inhibits proliferation and regulates lipolysis and lipogenesis processes in 3T3-L1 cells and isolated rat adipocytes. *Endocrine.* 2017;56:54-64.
105. Wahab F, Bano R, Jabeen S, Irfan S, Shahab M. Effect of peripheral Kisspeptin administration on adiponectin, leptin, and Resistin secretion under fed and fasting conditions in the adult male rhesus monkey (*Macaca mulatta*). *Horm Metab Res.* 2010;42:570-574.
106. Tolson KP, Marooki N, De Bond JAP, et al. Conditional knockout of kisspeptin signaling in brown adipose tissue increases metabolic rate and body temperature and lowers body weight. *FASEB J.* 2020;34:107-121.
107. Tsoutsouki J, Patel B, Comninou AN, Dhillo WS, Abbara A. Kisspeptin in the prediction of pregnancy complications. *Front Endocrinol (Lausanne).* 2022;13:942664.
108. Bowe JE, Hill TG, Hunt KF, et al. A role for placental kisspeptin in β cell adaptation to pregnancy. *JCI Insight.* 2019;4:4.
109. Zhou Q, Chen H, Yang S, et al. High-fat diet decreases the expression of Kiss1 mRNA and kisspeptin in the ovary, and increases ovulatory dysfunction in postpubertal female rats. *Reprod Biol Endocrinol.* 2014;12:1-11.
110. Zhai LL, Zhao J, Bai YL, Wei W, Sun Q, Jia LH. Combined effects of obesity and di-(2-ethylhexyl) phthalate on testosterone levels and kisspeptin/ GPR54 expression in hypothalamus and testes of male mice. *J Chin Med Assoc.* 2020;83:1020-1028.
111. Quennell JH, Mulligan AC, Tups A, et al. Leptin indirectly regulates gonadotropin-releasing hormone neuronal function. *Endocrinology.* 2009;150:2805-2812.
112. Ullah H, Nabi G, Zubair H, Ullah R, Shahab M. Age-dependent changes in the reproductive axis responsiveness to kisspeptin-10 administration in healthy men. *Andrologia.* 2019;51:e13219.
113. Nabi G, Ullah H, Khan S, et al. Changes in the responsiveness of the hypothalamic-pituitary-gonadal Axis to Kisspeptin-10 administration during pubertal transition in boys. *Int J Endocrinol.* 2018;2018:475967.
114. George JT, Milton JE, Cooper AE, Greentree S, Anderson RA, Holman RR. Stimulatory effects of the long-acting kisspeptin analogue TAK-448 on serum testosterone in men with type 2 diabetes and hypogonadotropic hypogonadism. *Diabetologia.* 2016;59:S228.
115. Blasco V, Pinto FM, Fernández-Atucha A, González-Ravina C, Fernández-Sánchez M, Cadenas L. Female infertility is associated with an altered expression of the neurokinin B/neurokinin B receptor and kisspeptin/kisspeptin receptor systems in ovarian granulosa and cumulus cells. *Fertil Steril.* 2020;114:869-878.
116. Li D, Wu Y, Cheng J, et al. Association of polymorphisms in the kisspeptin/GPR54 pathway genes with risk of early puberty in Chinese girls. *J Clin Endocrinol Metab.* 2020;105:E1458-E1467.
117. Kaya C, Alay İ, Babayeva G, et al. Serum Kisspeptin levels in unexplained infertility, polycystic ovary syndrome, and male factor infertility. *Gynecol Endocrinol.* 2019;35:228-232.
118. Abbara A, Jayasena CN, Christopoulos G, et al. Efficacy of kisspeptin-54 to trigger oocyte maturation in women at high risk of ovarian hyperstimulation syndrome (OHSS) during in vitro fertilization (IVF) therapy. *J Clin Endocrinol Metab.* 2015;100:3322-3331.
119. Izzi-Engbeaya C, Comninou AN, Clarke SA, et al. The effects of kisspeptin on β -cell function, serum metabolites and appetite in humans. *Diabetes Obes Metab.* 2018;20:2800-2810.
120. Comninou AN, Wall MB, Demetriou L, et al. Kisspeptin modulates sexual and emotional brain processing in humans. *J Clin Invest.* 2017;127:709-719.
121. Horikoshi Y, Matsumoto H, Takatsu Y, et al. Dramatic elevation of plasma metastatin concentrations in human pregnancy: Metastatin as a novel placenta-derived hormone in humans. *J Clin Endocrinol Metab.* 2003;88:914-919.
122. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. *Nat Rev Dis Primers.* 2019;5:5. doi:10.1038/s41572-019-0098-8
123. Yang L, Demetriou L, Wall MB, et al. The effects of Kisspeptin on brain response to food images and psychometric parameters of appetite in healthy men. *J Clin Endocrinol Metab.* 2021;106:E1837-E1848.
124. Pałasz A, Janas-Kozik M, Borrow A, Arias-Carrión O, Worthington JJ. The potential role of the novel hypothalamic neuropeptides nesfatin-1, phoenixin, spexin and kisspeptin in the pathogenesis of anxiety and anorexia nervosa. *Neurochem Int.* 2018;113:120-136.

How to cite this article: Sliwowska JH, Woods NE, Alzahrani AR, Paspali E, Tate RJ, Ferro VA. Kisspeptin a potential therapeutic target in treatment of both metabolic and reproductive dysfunction. *Journal of Diabetes.* 2024;16(4):e13541. doi:10.1111/1753-0407.13541