endocrines

Review

Kisspeptin Modulation of Reproductive Function

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Abstract: Kisspeptin is a peptide expressed mainly in the infundibular nucleus of the hypothalamus. Kisspeptin plays a crucial role in the regulation of reproductive functions. It is regarded as the most important factor responsible for the control of the hypothalamic–pituitary–gonadal axis, the onset of puberty, and the regulation of menstruation and fertility. Kisspeptin activity influences numerous processes such as steroidogenesis, follicular maturation, ovulation, and ovarian senescence. The identification of kisspeptin receptor mutations that cause hypogonadotropic hypogonadism has initiated studies on the role of kisspeptin in puberty. Pathologies affecting the neurons secreting kisspeptin play a major role in the development of PCOS, functional hypothalamic amenorrhea, and perimenopausal vasomotor symptoms. Kisspeptin analogs (both agonists and antagonists), therefore, may be beneficial as therapy in those afflicted with such pathologies. The aim of this review is to summarize the influence of kisspeptin in the physiology and pathology of the reproductive system in humans, as well as its potential use in therapy.

Keywords: kisspeptin; KNDy; kisspeptin analogs; kisspeptin antagonist; kisspeptin agonist; hypothalamus; neurokinin B

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Citation: Szeliga, A.; Meczekalski, B. Kisspeptin Modulation of Reproductive Function. *Endocrines* **2022**, *3*, 367–374. https://doi.org/10.3390/endocrines3030029

Academic Editor: Udo Jeschke

Received: 2 April 2022
Accepted: 22 June 2022
Published: 30 June 2022

1. Introduction

Kisspeptin is a peptide expressed mainly in the brain, within the hypothalamus (in humans, it is mainly found in the infundibular nucleus), and in the hippocampus [1]. Research has suggested that kisspeptin plays a crucial role in the regulation of reproductive functions. Kisspeptin is regarded as the most important factor responsible for regulating the onset of puberty, establishing mammalian reproductive functions, and regulating the hypothalamic–pituitary–gonadal axis. Kisspeptin activity influences numerous processes such as steroidogenesis, follicular maturation, ovulation, and ovarian senescence [2].

The identification of kisspeptin receptor mutations that cause hypogonadotropic hypogonadism has initiated studies on the role of kisspeptin in puberty. Pathologies affecting the neurons secreting kisspeptin (kisspeptin-neurokinin B-dynorphin neurons) play a crucial role in the developmental pathomechanism of vasomotor symptoms, PCOS, and functional hypothalamic amenorrhea. Therefore, the aim of this review is to summarize the influence of kisspeptin on the physiology and pathology of the reproductive system in humans [3,4].

2. Kisspeptin and Its Physiology

The reproductive system is driven by a myriad of complex interactions along the hypothalamic–pituitary–gonadal axis (HPG). In women, the executive organs of this axis are the ovaries (hypothalamus–pituitary gland—ovary axis; HPO). HPO is referred to as the pulsatile secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus, which in turn stimulates a pulsatile release of follicle-stimulating hormone (FSH) and, particularly, luteinizing hormone (LH) from the pituitary gland. These gonadotropins, in combination, exert a contributive action on ovarian steroidogenesis [5]. GnRH secreted in a pulsatile manner can be viewed as the main regulator of reproductive functions. GnRH

is itself also regulated through both direct and indirect pathways. This regulation of GnRH is achieved by a number of different neuropeptides and neurotransmitters such as galanin, neuropeptide Y, neurokinin B (NKB), nesfatin-1, kisspeptin, corticotropin-releasing hormone, norepinephrine and many others [6]. Among these, kisspeptin appears to play a pivotal role in the influence of reproductive function.

The history behind the discovery of kisspeptin and identification is quite sweet. *KISS1*, the gene responsible for encoding kisspeptin, was first identified in 1996 [2] and is located on chromosome 1q32. At first, the KISS1 protein was named *metastatin* due to its ability to suppress metastases. Initially a 145 amino acid precursor polypeptide, it is shortened to a length of 54 amino acids [7]. This peptide can be further split into short peptides of 4, 13, or 10 amino acids in length. These three short peptides are now recognized as kisspeptins, and their name is derived from the hallmark chocolate, which is manufactured at the Hershey chocolate factory located in Hershey, PA, USA, the town where the peptides were initially discovered [8].

Kisspeptins act on the G-protein coupled receptor 54 (GPR54) [9], which is encoded by gene *GPR54* in humans and is located on chromosome 16p13.3. The structure of *GPR54* is preserved across different vertebrates and has been labeled *Kiss1R*. In humans, *Kiss1R* is expressed mainly in the brain, in the hypothalamus (mainly the infundibular nucleus) but also in the hippocampus and anterior pituitary. Outside the brain, *Kiss1R* is expressed in the pancreas, liver, ovary, and adipose tissue [10].

Today, a lot of effort is being dedicated to defining the regulatory intricacies of kisspeptin secretion and its multifactorial action.

3. KNDy Neurons and Physiology of Hypothalamic Regulation of Reproductive Tract

Pulsatile GnRH secretion plays a critical role in regulating the reproductive axis (hypothalamus–pituitary–ovarian axis). GnRH secreting neurons in humans are primarily localized in the infundibular nucleus of the hypothalamus [11]. These neurons lead from the infundibular nucleus to the median eminence. At this anatomical site, GnRH is released in a pulsatile manner to stimulate the pulsatile release of gonadotropins (FSH and LH) [5].

From the initial discovery and identification of kisspeptin in the hypothalamus, significant research work has been undertaken to expand and understand the role of kisspeptin on GnRH release.

KNDy neurons in the infundibular nucleus are named for their co-expression of Kisspeptin, Neurokinin B (NKB), and Dynorphin (DYN) [12]. Groupings of KNDy neurons were first discovered in sheep in 2007. Similar clusters of neurons were subsequently identified in the human hypothalamus. Subsequent study has shown that KNDy neurons play a pivotal role in the regulation of GnRH neurons and their function [13].

It is now understood that NKB neurons and DYN neurons act as modulators of kisspeptin in its activity on GnRH secretion [14]. Specifically, NKB is responsible for kisspeptin secretion and, in turn, the downstream induction of GnRH release. In contrast, DYN neurons exert an inhibitory effect, suppressing kisspeptin secretion and, in turn, suppressing GnRH pulsatility [14].

The expression of KNDy neurons has been shown to differ between sexes. The use of immunochemistry and deep brain imaging techniques have been instrumental in revealing KNDy cell clusters and sexual dimorphism. The arcuate nucleus (ARC) in female subjects is characterized by a larger population of KNDy compared to male specimens. [15] This sexual dimorphism is not unique to humans but found in other species, such as monkeys and rodents as well.

The mechanism by which ovarian sex steroids modulate the function of KNDy neurons is crucial in understanding the broader role of these peptides. Beyond NKB and DYN receptors, Estradiol α receptors (ERα) and progesterone receptors (PR) are also expressed on KNDY neurons. This allows the KNDy neuron to act as a central integrator of systemic feedback for the reproductive system [8].

Ovarian steroids can thus modulate the expression of *KISS1* at the hypothalamic level. In turn, kisspeptin is responsible for the pulsatile release of GnRH. Ovarian steroids secreted in the early follicular phase have the ability to dampen GnRH release [16]. In contrast, estradiol produced in the late follicular phase will augment GnRH release, which in turn can provoke LH pulsatility [16].

4. Reproduction Depending on Kisspeptin Secretion

Kisspeptin is regarded as the most important factor responsible for the onset of puberty, for establishing mammalian reproductive functions, and for the regulation of the hypothalamic–pituitary–gonadal axis. The identification of kisspeptin receptor mutations that cause hypogonadotropic hypogonadism has initiated studies on the role of kisspeptin in puberty. The expression of *KISS1* and *KISS1R* has been found to be increased after puberty [17].

The expression of *KISS1* in the arcuate nucleus is increased during and following puberty. In Rhesus monkeys, it was found to correspond with an increase in LH release, while a central injection of kisspeptin in mammals was observed to cause a significant increase in GnRH release. Additionally, girls with precocious puberty have been found to have higher levels of kisspeptin [18].

Clarkson et al. [19] reported that the generation of GnRH pulsatility is dependent on KISS1 neuron activity at the level of the hypothalamus (specifically the arcuate nucleus). KISS1 neurons are responsible for releasing discrete calcium bursts, which strongly correlate with LH pulses [19]. Through this direct action on GnRH neurons, kisspeptin is involved in the promotion of puberty and maintaining fertility. Kisspeptin has, however, the ability to act on GnRH secretion through indirect mechanisms. This indirect action is via the mediated activation of glutamate and/or GABA afferent GnRH neurons [20].

It is important to consider the action of kisspeptin at the pituitary level. As previously mentioned, kisspeptin has the ability to stimulate the secretion of gonadotropins directly [21].

Kisspeptin exerts an essential stimulatory action in order to evoke the LH preovulatory peak, which is an essential component in ovulation. The action of kisspeptin with regard to reproduction descends all the way to the level of the ovary. Kisspeptin exerts an influence on processes such as steroidogenesis, follicular maturation, ovulation, and ovarian senescence [22]. Further studies, however, are required to elucidate all aspects of the mechanisms by which kisspeptin is involved in the physiology of reproduction [22].

5. Menopause Depending on Changes in KNDy Neurons

The postmenopausal decrease in serum 17-β-estradiol and the associated significant increase in serum FSH and LH are believed to be factors contributing to the development of vasomotor symptoms (VMS), which are symptoms connected with the postmenopausal period (hot flushes and night sweats) [23,24]. Nevertheless, the function of the hypothalamic–pituitary–ovarian axis at this time continues to be regulated by hypothalamic KNDy neurons. Recent trials have shown that the dysregulation of KNDy neurons is closely implicated in the etiology of somatic menopausal symptoms, notably hot flashes [25].

The hypertrophy of KNDy neurons in the hypothalamus (specifically in the infundibular nucleus) has been observed following menopause. These changes are associated with a subsequent increase in the secretion of neurokinin B and kisspeptin in the area. The increase in neuronal activity in this area is corroborated by an observed focal increase in the presence of the Nissl substance (reflecting an elevation in ribosomal RNA activity) and an enlargement of the nuclei [26]. Under microscopic examination, a 30% increase in the size of KNDy neurons was observed in this area. A similar process and appearance were observed in oophorectomized monkeys, an observation that suggests that ovarian impairment and the loss of estrogen negative feedback play a key role in this phenomenon [26].

LH pulses are synchronized with hot flashes in peri- and post-menopausal women [27]. While an increase in the serum LH concentration in women after menopause is a marker of

KNDy neuron hyperactivity, it also indicates that elevated kisspeptin or neurokinin B levels may play a crucial role in VMS pathogenesis. It has been shown that a central infusion with an NK3R agonist stimulates integumental vasodilatation, heat dissipation, and the development of hot flashes in rats [27]. Additionally, the destruction of KNDy neurons was associated with a decrease in skin vasodilatation. All of these observations support the hypothesis that KNDy neurons participate in the generation of hot flashes [23,28].

6. KNDy Neurons in Other Diseases

In a rat model of polycystic ovary syndrome (PCOS), a significant increase in the number of KNDy neurons was found when compared to healthy controls [29]. Similar studies have reported an increased expression of *TAC3* (gene coding for NKB) and KISS1 mRNA expression in the arcuate nucleus [30]. Patients with PCOS present with a significantly higher concentration of kisspeptin in the blood when compared to healthy controls [31–33]. When considering the stimulatory role that kisspeptin has on GnRH neurons and its ability to induce GnRH secretion, it is possible that it can induce and sustain LH pulse secretion [4,34]. A recent clinical trial in women with PCOS was conducted by George J.T. et al., who observed that a decrease in KNDy neuron activity could reduce LH secretion [35]. KNDy neurons can, therefore, potentially be exploited as a target for new agents to treat POCS.

Precocious puberty or premature thelarche (breast budding) have also been associated with elevated serum kisspeptin levels. These increased circulating levels of kisspeptin in patients with premature puberty strongly suggest that kisspeptin plays a pivotal role in the initiation of puberty [36–38].

Functional hypothalamic amenorrhea (FHA) is a disorder related to the decreased release of GnRH. As kisspeptin fundamentally impacts pubertal initiation and maturation along with the regulation of the reproductive axis, it has been suspected that abnormal concentrations of kisspeptin may be associated with the development of FHA. The mean serum concentration of kisspeptin in patients with FHA (0.17 ± 0.11 ng/mL) has been found to be significantly lower than that of control subjects (0.3 ± 0.36 ng/mL) [39].

7. Kisspeptin Analogs

7.1. Kisspeptin Agonists

Kisspeptin agonists and agonist analogs are increasingly used in the treatment of endocrinological disorders. The most important application of kisspeptin agonists is for the induction of ovulation in assisted reproductive technology. Treatment using in vitro fertilization (IVF) is an excellent alternative for couples struggling with infertility but is often limited by the risk of severe complications, such as ovarian hyperstimulation syndrome (OHSS) [40].

OHSS can lead to ovarian enlargement, hydrothorax, ascites, renal impairment, acute respiratory distress syndrome, and death [41]. Medications used for the induction of ovulation for oocyte retrieval in IVF protocols are the main causative factor of OHSS [42]. As a result of this, we continue to search for new drugs, which may reveal better treatment alternatives [43]. The use of kisspeptin in this regard may prove to be a safer alternative than the conventional IVF protocols used nowadays [40].

Kisspeptin has been shown to be involved in the stimulation of the preovulatory LH surge and is therefore required for ovulation. Kisspeptin analogs (such as kisspeptin-54) have demonstrated usefulness in inducing oocyte maturation in women undergoing IVF therapy. In a trial conducted by Jayasena C. et al., egg maturation was observed after the administration of kisspeptin-54. Additionally, the mean number of mature eggs observed per patient correlated positively with the administered dose of analog [44].

Owens et al. [45] undertook a head-to-head trial in which they compared kisspeptin-54 to the traditional drugs used to induce oocyte maturation. The serum FSH and LH measured after the administration of kisspeptin, when compared to conventional medications, more closely resembled that of a natural hormonal cycle. A recent study conducted by Abbara A. et al. indicated that although the LH surge following kisspeptin administration

was of lower amplitude than a conventional GnRH agonist, it is possible that kisspeptin enhances oocyte maturation via an additional action at the ovarian kisspeptin receptors through direct secondary action that compensates for the lower LH rise [46].

Abbara et al. [47] also studied kisspeptin-54 administration in sixty women who were at high risk of developing OHSS to investigate its ability to stimulate oocyte maturation antecedent to IVF. Ninety-five percent of the women treated in the study developed oocyte maturation, while no woman developed moderate, severe, or critical OHSS. This outcome further supports that kisspeptin-54 can be used as a viable alternative to stimulate effective and safe oocyte maturation in women at high risk of OHSS undergoing IVF treatment.

Beyond the use of kisspeptin agonists to stimulate ovulation, kisspeptin agonists show promise in the treatment of patients suffering from conditions associated with decreased LH secretion. Whitlock et al. [48] have examined the effects of kisspeptin and kisspeptin receptor agonists on plasma LH concentrations [48]. The administration of both was shown to produce a statistically significant elevation in serum LH levels in ewes. These results would suggest that kisspeptin agonists can be used in diseases such as hypothalamic amenorrhea. Jayasena C. et al. demonstrated that an intravenous infusion of kisspeptin-54 increases LH pulsatility in women with functional hypothalamic amenorrhea. This provides a promising basis for further investigation into the potential of kisspeptin-based therapies to treat women with FHA [49].

Kisspeptin was also examined in the context of puberty. Parker PA. et al. [50] examined the effects of the administration of analogs of kisspeptin in prepubertal bull calves. Kisspeptin was administrated in an acute and subacute manner. In both manners, the administration of kisspeptin analogs was associated with an increased LH concentration. On the other hand, kisspeptin analog subacute administration was associated with decreased FSH levels. It was concluded that because the subacute manner of the administration of a kisspeptin analog may decrease the FSH concentration, it may be useful to regulate the onset of puberty.

7.2. Kisspeptin Antagonists

The administration of kisspeptin antagonists was critical in unlocking the physiology of kisspeptin and explaining its function as it acts on the hypothalamus–pituitary–ovarian axis in animals. The administration of Peptide-234, a potent kisspeptin antagonist, decreases the mean GnRH concentration and inhibits spontaneous GnRH pulses in Rhesus monkeys. It was also shown to decrease LH pulses in ovariectomized sheep [51].

Kisspeptin antagonists have demonstrated potential and may have applications in clinical practice. The most evident application is in treating patients who suffer from diseases associated with increases in LH concentration, such as PCOS, postmenopausal symptoms, or precocious puberty [52]. The administration of a Peptide-234 infusion in pubertal female rats has been shown to induce the inhibition of uterine and ovarian development. Moreover, vaginal opening, which is an indicator of pubertal progression, was also delayed while not affecting body weight [53]. In women with PCOS, the normalization of GnRH secretion by kisspeptin and neurokinin B antagonists could decrease LH concentrations. This, in turn, would restore folliculogenesis and promote oocyte maturation [54]. In post-menopause, as in PCOS, GnRH and LH pulses are increased. Therefore, women who suffer from vasomotor symptoms during and while transitioning to menopause could likely benefit from some form of kisspeptin antagonist [54].

GnRH analogs are currently the only medication used in the treatment of precocious puberty. *KISS1* and *KISS1R* gene activating mutations have both been shown to cause precocious puberty [55]. Animal models of precocious puberty have also shown that the administration of kisspeptin antagonists has the potential to inhibit pubertal development. When considering the mounting information and progressively deeper understanding of the effects of kisspeptin, it is only reasonable to imagine it as a future therapeutic option for this group of patients [51].

8. Conclusions

Kisspeptin plays a crucial role in the regulation of reproductive functions. It is fast becoming apparent that kisspeptin is the most important factor responsible for supporting the onset of puberty and for establishing mammalian reproductive functions, as well as the regulation of the hypothalamic–pituitary–gonadal axis. Kisspeptin activity influences numerous processes such as steroidogenesis, follicular maturation, ovulation, and ovarian senescence. The identification of kisspeptin receptor mutations that cause hypogonadotropic hypogonadism has initiated studies on the role of kisspeptin in puberty. The pathology of kisspeptin-secreting neurons (kisspeptin neurokinin and B-dynorphin neurons) plays a crucial role in the pathomechanism of vasomotor symptoms, PCOS, and functional hypothalamic amenorrhea. Therefore, kisspeptin analogs (both agonists and antagonists) may be used in the treatment of such pathologies.

Author Contributions: Conceptualization B.M.; investigation A.S.; resources B.M. writing—original draft preparation B.M., A.S.; writing—review and editing B.M. supervision B.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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