Abstract

Since 2003, kisspeptin and its receptor (KISS1R, also called GPR54) are recognized as major actors of the gonadotrope axis. Mutations of genes encoding the peptide or the receptor have been identified in patients with precocious puberty or hypogonadotropic hypogonadism. They are strong stimulators of GnRH neurons and are involved in various mechanisms regulating gonadotrope axis as puberty induction or positive and negative feedback regulation on the gonadotrope axis by gonadal steroids. They also mediated some metabolic or environmental signals on the reproduction axis. Kisspeptins are synthesized and secreted by hypothalamic nuclei located in the arcuate nucleus (ARC) and anteroventral periventricular nucleus (AVPV). This system is complex because neurons located in the ARC coexpress many neuromediators such as neurokinin B and dynorphin, involved in the control of gonadotrope axis. During pregnancy, kisspeptins are also secreted by placenta and should be involved in trophoblastic invasion. After kisspeptin administration to male and female animals as well as to women with hypothalamic secondary amenorrhoea, they are able to stimulate GnRH and gonadotrophin secretion. Then, kisspeptin agonists appear as valuable new tools in treatment for reproduction troubles. The aim of this review is to clarify the role of kisspeptins in regulating gonadotrophin secretion and explores their possible therapeutic use.

1. Introduction

Studies reporting families with gonadotropin deficiency have led to a better understanding of the mechanisms regulating the hypothalamic–pituitary–gonadal axis. The characteristic features of the hypogonadotropic hypogonadism occurring in studied patients secondarily to gonadotropin-releasing hormone (GnRH) deficiency include late puberty and low serum levels of gonadotropins and sex steroids. The incrimented genes encode proteins that may be involved in GnRH neuron migration in the hypothalamus (KAL1, FGFR1, PROKFR2…), GnRH synthesis (GnRH1), or pituitary response to GnRH
Fig. 1. Products of the KISS1 (or kiss1) gene in humans and mice. KISS1 mRNA transcribed from the KISS1 gene is translated into a 138-aa peptide in humans and a 125-aa peptide in mice. This pre-pro-peptide is then cleaved into several active peptides (54, 14, 13, or 10 aa) sharing a common C-terminal region. The sequence of the amino acids, and particularly the 10 active amino acids, is highly preserved through evolution.

(GnRHR). In 2003, two teams simultaneously identified loss-of-function mutations of KISS1R (formerly GPR54), a gene encoding a 7-transmembrane domain G protein-coupled receptor, in patients with gonadotrophin deficiency without anosmia [1,2]. Kisspeptins are ligands of this receptor that were called metastatins when they were first identified in 2001 because of their implication in melanoma metastasis [3]. The initial product of the KISS1 gene encoding kisspeptins is a 145-amino acid (aa) peptide subsequently cleaved into a 54-aa peptide called kisspeptin-54 (Kp54). Shorter peptides, kisspeptin-10, -13, -14 (Kp10; Kp13; Kp14) sharing a common C-terminal region with kisspeptin-54 are also active (Fig. 1). In addition, other peptides closely related to kisspeptins, including neurokinin B (NKB) and dynorphin (Dyn), are emerging as regulators of the gonadotrope axis. A large body of work including clinical reports, animal models and cell culture studies has come forward since the discovery that KISS1R, its ligand, and these new neuropeptides, are highly implicated in human reproductive function, enabling a better understanding of the physiology and regulation of the kisspeptin/KISS1R couple and its role and importance in the regulation and secretion of GnRH.

2. Implication in human pathology

The first mutations of the KISS1R gene causing hypogonadotropic hypogonadism were discovered in 2003 [1,2]. To date, 13 loss-of-function mutations of KISS1R have been described in the literature [4]. These mutations are variable (large deletion, missense, nonsense, insertion . . . ), can involve one or two alleles, and are generally associated with hypogonadotropic hypogonadism. However, the depth of the GnRH deficit, the phenotype of the affected patients, and the response to exogenous GnRH are quite variable [5]. For instance in a consanguineous family described by de Roux et al. in 2003 [1], all siblings had the same homozygous mutation but presented different phenotypes: the four brothers exhibited complete hypogonadotropic hypogonadism with late puberty while their sister had partial hypogonadism with incomplete breast development and an episode of menstruation. The penetrance of KISS1R mutations and the genotype/phenotype correlation are variable. Moreover, one patient with two non-severe missense mutations developed complete hypogonadotropic hypogonadism [6]. Fertility is thus a fundamental question since these mutations are discovered in young or reproductive-age patients. The few data available on this topic have revealed the impact of KISS1R mutations on the reproductive capacities of mutated patients [5]. Long-term treatment with pulsed GnRH can normalize testosterone levels and induce spermatogenesis in mutated patients [7,8].

2.1. Mutations activating KISS1R

The kisspeptin/KISS1R couple is a powerful stimulator of the gonadotrope axis. Gain-of-function mutations of the KISS1R gene have been found in patients presenting central precocious puberty, the inverse phenotype of GnRH deficiency. The first patient described with a KISS1R-activating mutation was an 8-year-old girl adopted by a Brazilian family [9]. She developed idiopathic precocious puberty with slow progressive breast development from birth. An autosomal dominant mutation of the KISS1R gene (arginine-for-proline substitution in position 386) was demonstrated. The in vitro study showed that this mutation leads to prolonged activation of the signalization pathway in response to kisspeptins and a reduction in the desensitization of the mutated receptor. Recent studies have confirmed this mechanism by demonstrating that this mutation prolongs the response to kisspeptins by decreasing receptor degradation.
This mutation is thus a model of non-constitutive KISSR activation associated with precocious puberty.

## 2.2. KISS1 mutations

Data in the literature on KISS1 mutations have been highly controversial. Recently, two KISS1 mutations were identified in three unrelated children [11]. In one boy with a heterozygous P74S mutation, puberty development began at the age of 12 months. He was treated with gonadotropin analogs for 9 years. The second mutation, H90D, was identified as homozygous in two girls whose puberty started at the age of 6 years. The in vitro study of the mutated ligands suggests that they could play a role in precocious puberty in these patients [5]. However, this mutation has also been identified in a control cohort and in patients with idiopathic hypogonadotropic hypogonadism in French and American populations [12]. These findings suggest that this variant could be considered as a rare single nucleotide polymorphism (SNP). One other mutation, F117L, identified within the 10-aa active peptide in a woman with idiopathic hypogonadotropic hypogonadism without anosmia was shown to be deleterious by in vitro function tests, raising the question of its implication in the disease since the mother of the propositus was a healthy carrier [13]. The first inactivating mutation of KISS1 gene in humans has recently been reported [14].

## 2.3. TAC3 TACR3 mutations

In 2009, loss-of-function mutations of the TAC3 gene encoding NKB or the TAC3R gene encoding its receptor NK3R were demonstrated in patients with hypogonadotropic hypogonadism [15]. To date, about 40 patients have been described with TAC3 or TACR3 inactivating mutations [16]. Pulsed administration of GnRH in adult carriers of these mutations restores LH and testosterone secretion in men and induces ovulation with pregnancy and term birth in women [17]. These data suggest that the gonadotropic deficiency is secondary to deficient hypothalamic, rather than pituitary or gonadic, NKB signaling. NKB and kisspeptins are thus two recently emerged neuropeptides in the field of reproduction, particularly in the regulation of the gonadotropic axis. It has also been demonstrated that certain hypothalamic neurons expressing kisspeptins co-express NKB in several species including mice [18], goats [19], monkeys [20] and humans [21].

## 3. Animal models lacking functional kiss1 or its receptor

Studies in patients carrying KISS1R mutations have thus demonstrated the unexpected but primordial role of the kisspeptin/KISS1R system in regulating the gonadotropic axis. The demonstration that mice carrying a non-functional kiss1R or kiss1 gene reproduce the human phenotype provided supplementary proof in favor of a major role for this system in reproduction. Moreover, study of these animal models demonstrated that mammals display preserved kisspeptin regulation of the reproductive axis, leading to the discovery of the underlying mechanism.

### 3.1. Phenotypes of kiss1 or kiss1R knock-out mice

Mice with kiss1-/- and kiss1R-/- genotype perfectly reproduce the phenotype of patients with mutations inactivating KISS1R: abnormal sexual maturation with small sized genital organs and gonads, low levels of circulating gonadotropins and abnormal gametogenesis [22,23]. As observed in patients, the phenotypes of mutated mice are variable, sometimes with incomplete hypogonadotropic hypogonadism: some kiss1-/- or kiss1R-/- female mice present partial sexual maturation with vaginal opening signaling early puberty [24]. Gestation does not occur in kiss1 or kiss1R knockout mice [23]. Despite this sterility, kiss1-/- females can have estrous cycles, with estrus phases as well as spontaneous transitions from estrus to diestrus; the follicles can grow to the pre-ovulation phase but ovulation has not been observed [24]. Very recent and very disturbing results have shown that mice devoid of kisspeptin neurons develop normal puberty and are fertile [25]. This singular publication thus questions the primordial role of the kisspeptin/KISS1R system in controlling the gonadotropic axis and evokes a redundancy of the neuroendocrine system [25].

### 3.2. Mechanism

In the kiss1-/- mouse, migration of GnRH neurons in the hypothalamus normally occurs with their projection to the median eminence (ME) without any alteration of the contents of the GnRH neurons [22]. Conversely, the kiss1R-/- mouse displays a low level of circulating gonadotropins compared with control mice despite the lack of any significant difference in the total GnRH concentration in hypothalamic extracts [2]. These data suggest kisspeptins would have effect on GnRH release or pulsatility but not on its synthesis or production. The diversity of the phenotypes would be explained by the persistence of minute GnRH activity in kisspeptin or kisspeptin receptor knockout mice. Estrous cycles disappear totally in kiss1-/- or kiss1R-/- mice treated with GnRH antagonists [24].

### 4. Distribution of kisspeptins and their receptors

#### 4.1. Neuroanatomic localization of kisspeptin neurons

Several studies have been conducted in mammal models to localize the neurons expressing KISS1 in the central nervous system, essentially the hypothalamus. The murine model has been the most studied one. It has been established for several years that rodents have two main populations of kisspeptins localized in the arcuate nucleus (ARC) and the anteroventral periventricular nucleus (AVPV) [26]. Dispersed kisspeptin neurons have also been demonstrated in the brain, the amygdale, the striatum terminalis, and the paraventricular thalamus [27] but their physiological functions have not been clearly identified. In primates and humans, KISS1 mRNA is predominant in the infundibular nucleus, the equivalent of the arcuate nucleus in rodents [28].
Fig. 2. Neuroanatomic localization of kisspeptin neurons. Kisspeptin neurons are situated in two main regions of the brain: the arcuate nucleus (ARC) and the anteroventral periventricular nucleus (AVPV). Kisspeptins are active via their receptors on GnRH neurons (KISSR) mainly situated in the preoptic area inducing secretion of GnRH in the hypothalamo-pituitary portal system in the median eminence (ME). GnRH then activates the gonadotropic cells of the pituitary gland via their GnRHR, inducing secretion of LH and FSH, which in turn stimulate the gonads and induce the production of sex steroids. Males and females have an equivalent quantity of ARC kisspeptin neurons but females have many more AVPV kisspeptin neurons. The existence of this sexual dimorphism explains how the sex hormones exert both positive and negative feedback control of the hypothalamus: there are numerous ARC kisspeptin neurons relay the negative feedback control of the sex steroids in both sexes while there are very few AVPV neurons relaying the negative feedback control of estrogens in males and many in females.

4.2. Peripheral localization

Although the main role of the kisspeptin/KISS1R system is central, kisspeptins are also identified peripherally in the testes, ovaries, placenta, pancreas and small bowel. The greatest peripheral expression is observed in the placenta: serum levels of kisspeptins in pregnant women during the third trimester is about 7000-fold that observed in non-gestating women [30]. During gestation, several elements are in favor of an implication of the kisspeptin/KISS1R system in regulating trophoblastic invasion. For instance, the serum kisspeptin level is increased in patients with trophoblastic diseases and decreases after treatment [31]. Moreover, other studies show that the level of kisspeptins circulating in the maternal blood stream during the second trimester is lower during pregnancy associated with placental dysfunction (pre-eclampsia, intra-uterine growth retardation) [32]. The kisspeptin/KISS1R system would thus appear to be implicated in pregnancy but would not play a predominant role. Indeed, one patient with a KISS1R mutation had a normal pregnancy after treatment with GnRH and delivered a healthy child vaginally [8]. Complementary studies are needed to understand the role of kisspeptins during pregnancy as well as the usefulness of routine assay to predict placentation disorders [33].

5. Roles of the kisspeptin/kiss1r system

Since the discovery that kisspeptins and their receptor are implicated in triggering puberty, several studies have confirmed this role and also demonstrated other essential functions in the field of reproduction: mediators of positive and negative feedback control of GnRH secretion by sex steroids, integrators of diverse peripheral signals and powerful stimulators of GnRH secretion.

5.1. Trigger of puberty

Besides its major implication in the organization of neuron populations during the critical phase of sexual differentiation.
described above, hypothalamic kisspeptin neurons undergo a complex anatomic functional maturation at puberty [29]. Several elements are in favor of this functional activation. First of all, puberty cannot occur in humans and mice with a non-functional kisspeptin/KISS1R system [2]. More recently, it has been demonstrated that continuous intracerebroventricular infusion of a specific kisspeptin antagonist at the moment of pubertal transition alters the normal progression of puberty in the rat [34]. Finally, repeated administration of Kp10 in immature rats accelerates puberty onset [35]. Several intricate mechanisms enable activation of the hypothalamic kisspeptin/KISS1R system at puberty: increased expression of hypothalamic kiss1 with an increase in the number of kisspeptin neurons in the AVPV, increased apposition of kisspeptin neuron fibers with GnRH neurons, and greater sensitivity of GnRH neurons to kisspeptins [29].

5.2. Stimulator of GnRH secretion

Kisspeptins constitute one of the strongest stimulators of GnRH secretion in adults. A large number of studies have demonstrated that injection of kisspeptins can stimulate the secretion of GnRH and the pituitary gonadotropins LH and FSH [36]. An LH peak has been successfully induced in all species studied (rodents, sheep, monkeys, humans) irrespective of the administration route (intracerebroventricular, intravenous, subcutaneous) or the size of the peptide (Kp10, Kp13, Kp54), even at very low doses [37]. Several elements point to GnRH neurons as the main sites of action of kisspeptins [38]. First, GnRH neurons express the kisspeptin receptor KISS1R; second, when animals are pretreated with GnRH antagonists, kisspeptin-induced LH and FSH release is blocked. Furthermore, in vitro, kisspeptins induce GnRH secretion by rat hypothalamic explants [39].

5.3. Mediator of positive feedback control

Among the regulators of the gonadotropic axis, sex steroids play a major role in controlling GnRH secretion. The effect of these steroids is sexually dimorphic and depends on the physiological status. Estrogens for instance can induce a peak in LH secretion, but uniquely in females and uniquely in a precise phase of the ovarian cycle, provoking ovulation; this is positive feedback control. Using antagonists of the alpha estrogen receptor (ERα), it has been demonstrated that this feedback control is mediated via the ERα and not the second type of estrogen receptors ERβ [40]. But GnRH neurons express ERβ and not ERα [41], suggesting there would be an intermediary pathway relaying the estrogen action on GnRH neurons. Kisspeptin neurons in the AVPV are more numerous in females than males, express ERα, and project on GnRH neurons, making them ideal candidates for this intermediary pathway [42], which has been demonstrated in several rodent models. It has been shown that estrogens induce increased expression of kisspeptin neurons in the AVPV, that the same neurons are activated during the pre-ovulatory period, and that blocking endogenous kisspeptins in the pre-optic area abolishes the LH peak in the rat [38].

While the AVPV kisspeptin neurons are implicated in the positive feedback control of GnRH secretion by estrogens, the ARC kisspeptin neurons are implicated in the negative feedback control by sex steroids. This neuron population has been demonstrated with ovariectomized animals in rodents, the concentration of kiss1 mRNA in the ARC is increased when sex steroids are inhibited and this increase is prevented by estrogen or testosterone replacement therapy [44]. This negative feedback control has also been demonstrated in primates [45] and in menopausal women who display increased KISS1 expression in the infundibular nucleus (human equivalent to the ARC) [28]. The more recent studies have implemented much more complex protocols than this binary model because ARC kisspeptin neurons would also secrete other neuromediators (NKB and Dyn) involved in regulating the gonadotropic axis [18].

5.5. Integrator of diverse metabolic and environmental signals

Energy reserves and metabolic status also play a major role in regulating the gonadotropic axis. Leptin, a hormone secreted by adipocytes, is one of the main endocrine mediators involved in regulating metabolic status and energy stocks, as well as reproduction by signaling the organism’s energy status to the neuron centers of reproduction. In humans, a leptin deficiency, whether related to an energy deficit as in anorexia nervosa or restrictive food intake disorder, or to a mutation of leptin or its receptor, and in ob/ob leptin-deficient mice, leads to reproductive disorders secondary to hypogonadotropic hypogonadism [46,47]. Leptin receptors have not been visualized in vivo on GnRH neurons [48] but on the contrary have been in mice where a large proportion of the ARC kisspeptin neurons express an active form of the leptin receptor [49]. Expression of kiss1 mRNA is influenced by the animal’s nutritional status: in fasting male and female puberal mice a significant fall in kiss1 mRNA is observed with a concomitant fall in circulating LH [50–52]. Similarly, there is a reduced expression of kiss1 in the ARC nucleus of ob/ob mice compared with controls. Most likely, kisspeptin neurons play a leading role in the hypothalamic relay of leptin signaling and more widely in energy metabolism regulation of GnRH secretion. However this leptin/kisspeptin/GnRH pathway does not appear to be exclusive.

In some species, the kisspeptin/KISS1R couple also modulates the impact of season on reproduction, a phenomenon studied in hamsters and sheep. Reproduction is tightly regulated by the photoperiod in animal species with seasonal reproductive patterns. Hamsters reproduce when day length becomes longer and enter a quiescent phase of reproduction when day
Fig. 3. Roles of the kisspeptin/KISS1R system. Kisspeptins are major elements of the gonadotropic axis and are implicated in many pathways regulating the gonadotropic axis. The feedback control of the sex steroids as well as the metabolic and environmental signals have a direct effect on kisspeptin neurons.

length becomes shorter [53]. Kisspeptins are expressed in the ARC nucleus in these mammals but during the period when day length is short their expression is inhibited in this region of the brain [54,55]. Conversely, in sheep, reproduction basically coincides with the time of year when daytime shortens, the females entering anestrus in winter. In these animals, expression of kiss1 is increased in the ARC nucleus during the period of short day length in ovariec-tomied females, but there is no seasonal variation in kiss1 expression in the pre-optic area. These experiments suggest that kisspeptins would play a major role not only in invoking puberty but also in the seasonal regulation of the gonadotropic axis.

Pathways modulating the gonadotropic axis via kisspeptins are illustrated in Fig. 3.

6. Molecular and cellular mechanisms

In vivo and in vitro injections of kisspeptins have been used to demonstrate the powerful stimulating effect of these neuropeptides on GnRH neurons. The site of action of kisspeptins on the GnRH neurons (cell body, nerve terminals) and mode of the effect on GnRH secretion (induction, release, stimulation) are still the subject of much debate. The fact that ARC kisspeptin neurons also co-express other neuromediators implicated in regulating the gonadotropic axis (NKB, Dyn) further complicates the molecular analysis of the activation mode of GnRH neurons (Fig. 4).

6.1. Mechanism of action

GnRH neuron cell bodies are widely diffused in the preoptic area of the hypothalamus and project to the median eminence (ME). GnRH is released in pulses in the ME into fenestrated capillaries of the hypothalamo-pituitary portal system then transported to the pituitary gonadotropic cells where it stimulates production and secretion of LH and FSH. Generation of GnRH pulses in the ME is the central and essential element regulating reproductive function. It is now well established in several species that kisspeptins, secreted in pulses [19], can stimulate GnRH secretion and induce a peak in LH. Nevertheless, the mechanism by which kisspeptins stimulate GnRH secretion remains unclear. One of the first studies which recognized kisspeptins and their receptor as fundamental elements of the gonadotropic axis showed that there is no difference in GnRH concentration in the hypothalamic extracts of kiss1R knock-out mice and control mice, while the circulating level of LH is significantly reduced in knock-out mice [2]. These results are not in favor of a kisspeptin action on GnRH production. One possible hypothesis would be a direct action of kisspeptins on GnRH release and pulsatility. Intracerebroventricular administration of kisspeptin or its antagonist in the ARC or the preoptic area (including the AVPV) has demonstrated that ARC kisspeptin neurons modulate the frequency and amplitude of LH pulses [56]. Other studies using rat hypothalamic explants have demonstrated a stimulation of GnRH release secondary to a direct action of kisspeptins on the nerve terminals of GnRH neurons [39,57–59]. According to these studies, kisspeptins
Fig. 4. Schematic representation of the role of KNDy neurons in the generation of GnRH pulses. In this model, KNDy neurons are controlled by neurokininB and dynorphin via autosynapses. They project to the axons of the GnRH neurons in the median eminence which has receptors for NKB and kisspeptins. The KNDy neurons are the most effective stimulators of GnRH secretion.

Adapted from Navarro et al. The Journal of Neuroscience, 2009 [18].

would appear to act directly on the nerve endings of GnRH neurons in the ME to control GnRH release, pulsatility, or discharge. However, this mechanism remains controversial. One in vitro study demonstrated that cell lines expressing kiss1R treated with kisspeptins increase GnRH secretion as well as the level of mRNA [60].

6.2. Site of action of kisspeptins on GnRH neurons: cell body and/or nerve endings

In order to elucidate the mechanism of action of GnRH secretion secondary to stimulation by kisspeptins, several teams have attempted to demonstrate the interactions occurring between kisspeptins and GnRH neurons. All of the studies confirm that GnRH neurons express kiss1R, but some are in favor of an expression by the neuron cell body [61] while others would demonstrate receptor expression solely at the nerve endings [57]. One of the hypotheses favors the GnRH neuron cell body while the majority of the projections of the ARC neurons regulating GnRH release via kisspeptins/neurokininB and Dyn would be in the ME [62]. Accordingly, positive feedback control of GnRH secretion by sex steroids would affect the cell bodies of neurons secreting GnRH while the negative feedback control would affect the nerve terminals of these same neurons [62].

6.3. KNDy neurons

The ARC kisspeptin neurons co-express NKB and Dyn and are called KNDy neurons. This co-localization is strongly preserved in mammals, including humans [16,21]. Dyn is an endogenous opioid peptide known for its role in negative feedback control of GnRH secretion by progesterone [63]. Dyn acts via the κ opioid receptor (KOR). NKB, encoded by the TAC3 gene in humans and tac3 in rodents, is a member of the tachykinin family implicated in regulating the gonadotropic axis [16] via its receptor NK3R (encoded by the TAC3R gene in humans and the tac2r gene in rodents). The effects of NKB on gonadotropic axis regulation in sheep and rodents are controversial [64]. It has nevertheless been recently demonstrated that administration of NKB or senktide, an NK3R agonist, induces an LH peak in rats, sheep and monkeys [20,65,66]. Expression of the gene encoding NKB and the effect of NKB on gonadotropin secretion appear to be steroid-dependent [29]. Indeed, ovariectomy increases expression of the gene encoding NKB in the ARC nucleus in several species including the mouse [18], while treatment of these gonadectomized animals with estrogen suppresses expression of this gene; furthermore senktide inhibits LH secretion in ovariectomized animal models [65]. NKB appears thus to modulate GnRH secretion under certain conditions; the KNDy neurons are a fundamental element in regulating pulsatile secretion of kisspeptins and thus control secretion of GnRH in the median eminence [18,19,67].

7. Implications in humans

Current understanding of the mechanisms implicating kisspeptins in the regulation of the gonadotropic axis suggests the possibility of using these molecules for therapeutic purposes.
Several studies conducted in healthy volunteers or patients have been encouraging (Table 1).

### 7.1. Studies in healthy volunteers and patients with hypogonadotropic hypogonadism

In healthy male volunteers, a 90-minute intravenous infusion of Kp54 induces a significant increase in the serum levels of LH, FSH and testosterone [68]. Similarly, two recent studies have shown that an intravenous bolus of Kp10 can trigger an immediate increase in LH [69,70]. Similar studies in healthy women has shown that subcutaneous injections of Kp54 provoke a marked elevation in circulating LH that is more pronounced than observed in the pre-ovulatory phase of the menstrual cycle [71]. Despite the vasoconstrictor properties demonstrated in vitro [72], subcutaneous or intravenous administration of kisspeptins in humans does not provoke any secondary effect [68,71]. Several teams have attempted to treat patients with hypogonadotropic hypogonadism. For instance, infertile women with functional hypothalamic amenorrhea (FHA) have been treated with twice daily or twice weekly subcutaneous injections of Kp54. Administration of this compound induced a stimulation of gonadotropin secretion [73,74]. Furthermore, it has been demonstrated that in these women, the increase in the LH response to Kp injections is greater than that observed in the follicular phase in healthy volunteers. This would be due to an explosive
response to kisspeptins in women with functional amenorrhea or to an increased sensitivity to the effects of GnRH [42]. Similarly, injections of Kp10 restore pulsatile gonadotropin secretion in patients with congenital hypogonadotropic hypogonadism by mutation of NKB and its receptor NK3R [75].

7.2. Receptor desensitization

In healthy men a 22-h continuous infusion leads to higher testosterone levels and LH pulses enhanced in both frequency and amplitude [69]. However, a mechanism of kisspeptin receptor desensitization is likely since in women with hypothalamic amenorrhea, several weeks of twice daily subcutaneous injections of kisspeptins causes a marked stimulation of gonadotropin secretion just after the first injection followed by a significant decline after two weeks of the same treatment [73]. In addition, twice weekly injections of Kp54 in patients with the same pathological situation maintains the gonadotropin response to kisspeptin injection for at least eight weeks. This mechanism of receptor desensitization has also been demonstrated in several animal models [74].

7.3. Possible therapeutic uses

Gonadotropin injections (LH and FSH) constitute the classical treatment for infertility. Kisspeptin injections, which stimulate secretion of endogenous GnRH inducing increased secretion of endogenous gonadotropins from the pituitary gland, could be a new element of the therapeutic armamentarium for medically assisted reproduction. This more physiological stimulation of endogenous gonadotropins might reduce the risk of overstimulation of the ovaries often associated with excessive injections of exogenous gonadotropins. In addition, this treatment might be useful for patients with mutations inactivating KISS1R, NKB, or NK3R. Kisspeptins could also be used as an integral part of the treatment for retarded puberty. The existence of a desensitization mechanism affecting the receptor might also have implications for the use of kisspeptins in the treatment of endometriosis or steroid-sensitive tumors.

Complementary studies are needed to evaluate the risks and benefits of this type of treatment in different pathological conditions.

8. Conclusion

Kisspeptins and their receptor are now recognized as major elements of the hypothalamo-pituitary-gonadal axis. They are powerful stimulators of GnRH secretion and are implicated in diverse signaling pathways regulating the gonadotropic axis. In addition, kisspeptin injections have been used effectively without producing adverse effects in healthy volunteers and infertile patients. They would now represent a new element in the therapeutic armamentarium for disorders of reproductive function.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


