Current Highlights

The role of kisspeptin signalling in control of reproduction in genetically similar species

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ABSTRACT

Kisspeptin (previously known as metastin) is a protein encoded by the KISS-1 gene in humans. Kisspeptin producing neurons seem to bridge the gap between the sex steroid levels and feedback mechanisms that control the gonadotropin releasing hormone secretion. Since 2003, there are many studies on the facets of neuroendocrine networks that control puberty and fertility. These have explored the role of Kisspeptins in puberty and fertility using animal models. Kisspeptins are universally recognized as essential activators of the gonadotropic axis and they play an essential role in the metabolic regulation of fertility. Moreover, novel aspects of Kisspeptins/G-protein coupled receptor 54 or Kisspeptin receptor (KPs/GPR54) physiology have demonstrated the Kisspeptins involvement in the neuroendocrine control of ovulation. In this article, the authors highlight the outcome of the most recent work on Kisspeptin role in reproduction in human and animal models and give an opinion on future perspectives.

Keywords:

Axis; gonadotropins; gonadal; hypothalamus, Kisspeptin; pituitary; puberty; signalling.

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INTRODUCTION

Kisspeptin, encoded by KISS-1 gene, is a protein produced by human brain and also in other genetically similar species. It has a fundamental role in reproduction. The Kisspeptin producing cells predominately populate the anteroventral periventricular nucleus (AVPV) and the arcuate nucleus (ARC) in rodents. KiSS1 gene encodes the kisspeptin family of overlapping peptides that with their receptors play a crucial role in puberty period and fertility including central activation of the hypothalamic-pituitary-gonadal axis at puberty. Kisspeptins were originally characterised as potent anti-metastatic agents in breast cancer and malignant melanoma cells [1]. One member of this kisspeptin family of arginine-phenylalanine amide peptides, KP-54, was subsequently identified as the natural ligand for the kisspeptin receptor (previously known as G protein-coupled receptor 54 (GPR54)) [1]. Though this system is now considered as a fundamental player in the reproductive brain, the role of Kisspeptins and GPR54 in the control of puberty and fertility remained unknown until late 2003, when de Roux et al. and Seminara et al. and co-workers, independently, reported deletions and inactivating mutations of GPR54 in patients with idiopathic hypogonadotropic hypogonadism (IHH) [2,3]. Mutations in KP/GPR54 system that interfere with Kisspeptins signalling prevent normal pubertal development in humans and mice [4]. Failure of the GPR54 and KiSS1 mutant mice to ovulate has led to the suggestion that Kisspeptins signalling may be required for the pre-ovulatory luteinizing hormone (LH) surge [4].

Since 2003, many studies of the aspects of neuroendocrine networks, which control puberty and fertility through KPs/GPR54 system have been explored using animal models such as: rodents, sheep, primates and pony mares [5]. After intensive research activity recently, the role of KPs in reproduction can be summarized as follows [6]:

1. Kisspeptins are universally recognized as **essential activators of the gonadotropin axis:** with key roles in puberty onset and control of gonadotropin secretion.

2. Novel aspects of KPs/GPR54 physiology have emerged, including their involvement in t**he neuroendocrine control of ovulation.**

3. Kisspeptins play an essential role in the **metabolic regulation of fertility (as fundamental gatekeepers of reproduction).**

Moreover, a **'comparative endocrinology'** of this system has also been explored recently.

In addition to KP/GPR54 role in reproduction and besides the anti-metastatic function, the expression of Kisspeptins in other tissues such as human placenta, pancreatic islet cells, aorta, coronary and umbilical vessels as well as number of brain cells suggested other different roles of Kisspeptins, which are beyond the scope of this focused task.

ACTIVATION OF GnRH AXIS

Control of Gonadotropin release:

Compelling evidence demonstrates that Kisspeptins are able to directly activate hypothalamic GnRH neurons, as a major mechanism of action for their potent effects in terms of induction of gonadotropin release (Figure 1) [6]. The KP/GPR54 system is mainly involved in the dynamic control of the GnRH system, where its function appeared to be the "shut-down" of the whole system in conditions of defective GPR54 signalling [7], a condition known as normosmic isolated hypogonadotropic hypogonadism (nIHH). Further evidence of the capacity of Kisspeptins to stimulate GnRH secretion at the hypothalamus came from functional and neuroanatomical studies on animal models [8-10].

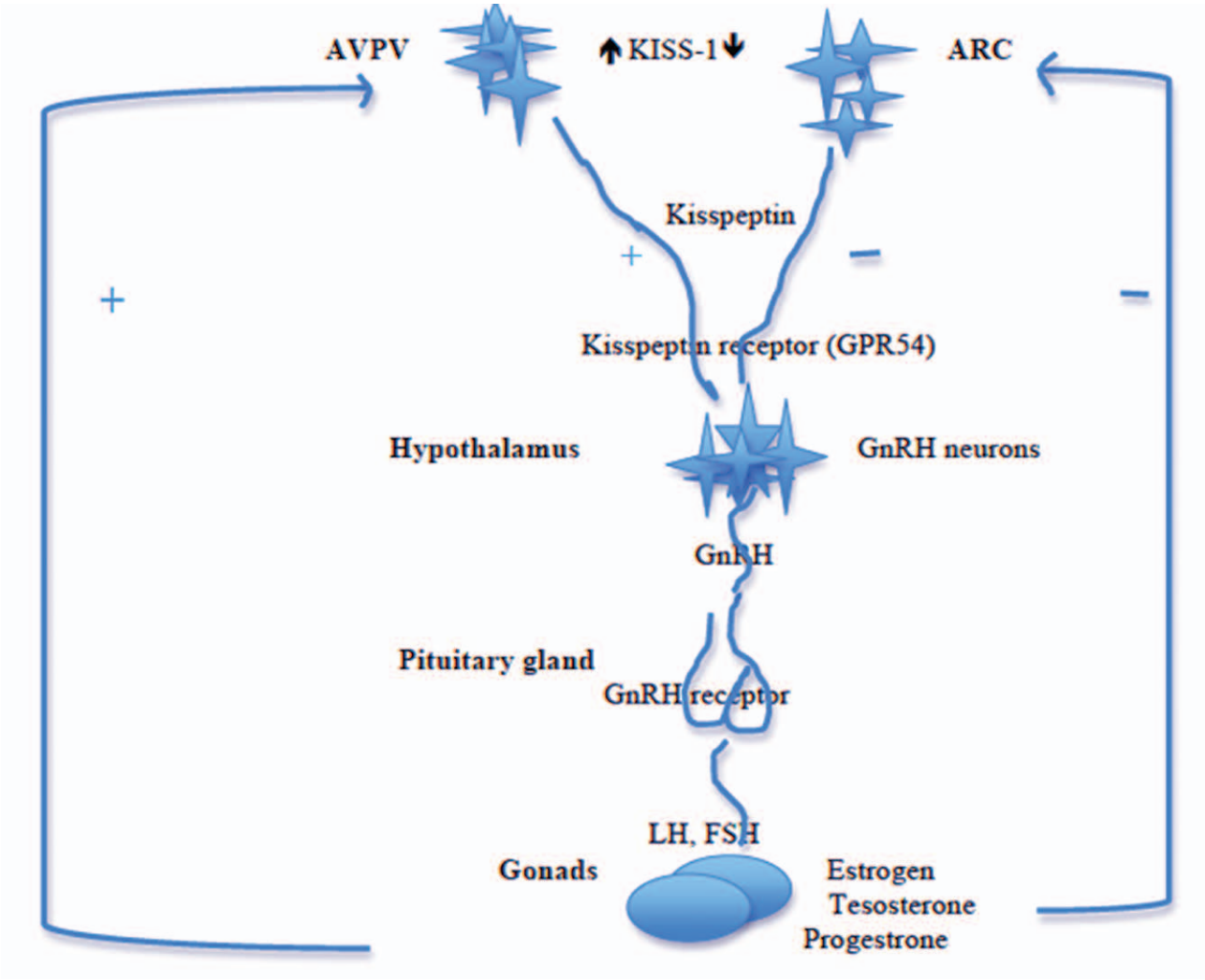

Figure 1 - Role of Kisspeptin signalling in hypothalamic pituitary gonadal axis

ARC– Arcuate nucleus; AVPV- anteroventral periventricular nucleus; FSH- Follicular stimulating hormone; GnRH- Gonadotropin releasing hormone; GPR54- G-protein coupled receptor 54; KISS-1- Kisspeptin gene; LH- Luteinizing hormone.

A potent stimulatory effect of KP-10 and metastin on LH secretion was demonstrated in human and different animal species [11-18]. In addition, pharmacological analysis demonstrated that Kisspeptins when administered via variable routes, result in LH secretion at different stages of postnatal development (infantile and juvenile periods in the rat and mouse) [19,20]. However, despite preserved responsiveness to GnRH, GPR54 null mice failed to secrete LH in response to KP-14 administration, suggesting that the gonadotropin-releasing effects of Kisspeptins are solely mediated via GPR54 [17].

FSH secretion also responds to Kisspeptins administration. Though FSH response was found to be somewhat delayed (from 30-min onwards) as compared to the rapid LH response (within 5–15-min) [21]. The mechanisms for such divergence remained unknown, but they might involve the following: (i)

FSH secretion being more constitutive than that of LH; (ii) The effects of Kisspeptins on the pattern of GnRH release, with the predominant activation, which favours LH secretion; and/or (iii) differences in the regulatory actions of peripheral factors (mainly gonadal peptides, such as inhibins) that selectively impinge on FSH secretion [6]. In any case, the above observations pose obvious pharmacological implications (e.g., design of protocols of selective activation of LH secretion) [6]. The patterns of FSH responses to KP-10 appear to diverge between male (delayed but long-lived) and cyclic female (rapid but of shorter duration) rats [6].

Further evidence for the physiological relevance of the hypothalamic KP/GPR54 system in the control of the gonadotropic axis was provided by expression analyses in models of gonadectomised animals [6]. Sex steroid replacement of gonadectomised rats (testosterone in males; estradiol in females) totally prevented both hormonal (LH and FSH) and gene expression (KiSS-1) responses [13]. These data were later refined by in situ hybridization analyses in rodents, which showed that sex steroids are able to repress KISS-1 gene expression selectively at the ARC [22,23]. These findings clarified that KiSS-1 neurons at this hypothalamic site are under the regulation of sex steroids and probably operate as an important relay for conveying the negative feedback actions of androgen and oestrogen on gonadotropins secretion [24]. However, this aspect of the function of KISS-1 system was found to be more complex, and KISS 1 system was also involved in mediating the positive feedback actions of oestrogen on LH secretion at the pre-ovulatory period in female menstrual cycle.

Role in puberty onset:

KP/GPR54 system plays a central role in puberty onset. This was already evident by the reproductive phenotypes of humans and mice with null mutations of GPR54, which showed a state of sexual immaturity [25, 26]. Overall, the mechanism whereby this system participates in the onset of puberty may include, at least, four major components [6]:

i. An increase in the endogenous Kisspeptins tone, which, if sufficient, can drive the GnRH/gonadotropin axis to a state of full activation.
ii. An elevation in the sensitivity to the stimulatory effects of Kisspeptins in terms of GnRH/LH responses
iii. An enhancement of GPR54 signalling efficiency coupled to a less consistent increase in GPR54 expression
iv. An increase in the number of Kisspeptins projections to GnRH neurons from specific hypothalamic areas (e.g. AVPV). The latter phenomenon appears relevant for the precise timing of puberty, as GnRH/LH responsiveness to Kisspeptins is present at earlier stages of postnatal development [9,19].

ROLE IN OVULATION

KPs influence HPG axis mainly at the level of hypothalamus. However they also influence the axis at the pituitary and ovaries levels. Initial expression analyses failed to provide direct evidence for generation of the pre-ovulatory surge as a role of KiSS-1, as oestrogen appeared to inhibit (negative feedback) rather than stimulate (positive feedback) the hypothalamic expression of KiSS-1 gene [27]. Further pharmacological and functional investigations and in situ hybridization analyses, have now substantiated a fundamental role of KP/GPR54 in the cyclic female; the major characteristics of this key function are as follows [6]:

- KiSS-1 neurons in the AVPV were shown to behave in an opposite manner, i.e. expression of KiSS-1 gene at this hypothalamic site markedly increased following oestrogen replacement and decreased following gonadectomy [22,23]. This was the first evidence to suggest that KiSS-

1 neurons at this site might be involved in the generation of the pre-ovulatory gonadotropin surge, at least in rodents. The mechanisms for the generation of the pre-ovulatory surge of gonadotropins are likely to differ between rodents and primates and therefore it is yet to be well defined in human.

- In ovariectomised female rats, standard oestrogen and progesterone priming induced not only the expected surge of LH levels but also enhanced KiSS-1 expression at the AVPV [28].
- Responsiveness to endogenous Kisspeptins is an additional source for cyclic changes in gonadotropin secretion in the female besides fluctuations in KiSS-1 expression at certain hypothalamic nuclei. KP selectively induces maximal LH secretion during the transition of proestrus to oestrus. A window of maximal effectiveness for the LH-releasing effects of Kisspeptins is likely defined by changes in the sex steroid milieu at certain stages of the cycle. Overall, this propose that, in the presence of activated progesterone receptors, a rise in oestradiol evokes a state of hyper-responsiveness to Kisspeptins contributing to the generation of the pre-ovulatory surge of gonadotropins.
- A dramatic increase in circulating levels of Kisspeptin (first named metastin) has been reported in pregnant women [29], despite the suppression of circulating gonadotropin levels detected during gestation in human [30]; which suggested a state desensitization of gonadotropin responses after exposure to persistently elevated levels of Kisspeptins Though this was not found to be the same in the research on rats.
- Changes in Kisspeptins signalling might be relevant for the suppression of the gonadotropic axis during lactation. The mechanisms may include:
  - A significant suppression in the sensitivity of the gonadotropic system to Kisspeptins stimulation
  - A decrease of the endogenous Kisspeptins tone at some hypothalamic areas (e.g. ARC).
- Early developmental events driven by gonadal steroids during critical periods of sexual differentiation of hypothalamic KiSS-1 system plays a role in the pre-ovulatory surge: The development of KiSS-1 neurons at the AVPV, but apparently not at the ARC, is sensitive to the organizing effects of sex steroids during the neonatal period of sexual maturation of the brain.
- The ability of the LH surge to timely induce the ovarian expression of KiSS-1 gene at the pre-ovulatory period suggests that locally produced Kisspeptins might be involved in the control of some aspects of ovulation. Though the major site of action of KP/GPR54 in regulation of ovulation is located at the hypothalamus.

METABOLIC REGULATION OF FERTILITY

Reproduction is directly related to energy reserves and the metabolic status of the organism; sufficient energy stores and proper metabolic status are mandatory for fertility. Kisspeptins plays an essential role in the metabolic regulation of fertility. In negative energy balance conditions an expression of KiSS-1 gene is decreased [31].

The potential role of the hypothalamic KiSS-1 system in conveying information regarding metabolic and energy status was originally based in two premises [6]:

i. Conditions of altered energy homeostasis or metabolism known to have an impact on the gonadotropic axis should influence also the expression of KiSS-1 at the hypothalamus
ii. Exogenous administration of Kisspeptins in states of metabolic impairment should ameliorate or totally rescue defective gonadotropic function in those conditions.

These assumptions have been now supported by several lines of evidence from studies on uncontrolled diabetics and leptin deficient organisms [32-36].

POTENTIAL THERAPEUTIC ROLE AND FUTURE PERSPECTIVES

Inactivating GPR54 mutations cause nIHH in humans. Equivalently, activating mutations, which increase GPR54 signalling are related to onset of gonadotropin-dependent precocious puberty. Therefore, possible therapeutic role of KP administration has been discussed. Kisspeptins might be used to manipulate the HPG axis in humans. However, further studies are essential to reveal the exact mechanism and role of GPR54 agonists and antagonists' applications [31].

Here, we discussed key KP/GPR54 discovery events and present an evolution of Kisspeptins biology in recent animal and human research work. With evidence pointing to proper KP/GPR54 signalling as the principal trigger for activation of GnRH neurons and subsequent ovulation, elucidation of how this pathway is modulated is likely to bring novel pharmacologic strategies for fertility treatment (and contraception) within reach [1].

Recent neuroanatomical investigation has identified key "KNDy" (Kisspeptin, Neurokinin B, Dynorphin) arcuate neurones that are conserved amongst different species and that are intimately connected both to each other and to the GnRH nerve termini [37]. Even after the discovery of mutations in the Kisspeptins receptor as a cause of nIHH, up to 70% of cases of nIHH could not be explained by any known genetic defect [38], suggesting that there were further insights into the function of the GnRH pulse generator to be explored. This has recently been borne out by discovery of mutations in the genes encoding either neurokinin B (NKB) or its receptor, the neurokinin 3 receptor (NK3R) as causes of nIHH [39]. This has helped to inform subsequent research in model organisms, as well as providing insight into another key component of the GnRH pulse generator [37].

CONCLUSION

Kisspeptins have important functions in the control of reproductive axis, which appear to be conserved between humans and rodents. There is strong evidence that KPs/GPR54 system is involved in sexual development and the control of puberty onset. Kisspeptins serve as a vital link between the reproduction and energy homeostasis of the body. The potential therapeutic uses include the treatment of infertility and reproductive disorders in humans including precocious or delayed puberty and ovarian function modulation. Further research of the KiSS1/Kisspeptin/GPR-54 system is needed to allow reliable generalization of the available research findings in human and genetically similar animal models.

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