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Kisspeptin and KISS1R: a critical pathway in the reproductive system

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Abstract

In 2003, three groups around the world simultaneously discovered that KISS1R (GPR54) is a key gatekeeper of sexual maturation in both mice and men. Developmental changes in the expression of the ligand for KISS1R, kisspeptin, support its critical role in the pubertal transition. In addition, kisspeptin, a powerful stimulus of GNRH-induced gonadotropin secretion and may modulate both positive and negative sex steroid feedback effects at the hypothalamic level. Genetic studies in humans have revealed both loss-of-function and gain-of-function mutations in patients with idiopathic hypogonadotropic hypogonadism and precocious puberty respectively. This review examines the kisspeptin/KISS1R pathway in the reproductive system.

Introduction

Human puberty is a mystifying process involving a complex series of hormonal events. The onset of puberty is marked by an increase in the secretion of gonadotropin-releasing hormone (GNRH) from the hypothalamus. Pulsatile secretion of GNRH triggers the release of the gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland that in turn stimulates the production of sex steroids by the gonads. Sex steroids exert negative feedback effects at both the hypothalamus and pituitary with the exception of estrogen that undergoes positive feedback at the time of the mid-cycle ovulatory surge.

Studies conducted in the 1980s and 1990s identified some of the central players in the inhibitory and stimulatory controls of the GNRH pulse generator (Kaufman *et al*. 1985, Terasawa & Fernandez 2001, Grumbach 2002, Ojeda *et al*. 2003, Plant & Barker-Gibb 2004). It seems likely that a large number of different neurotransmitters are involved in modulating the behavior of the GNRH neuron (Todman *et al*. 2005). The GABAergic neuronal system appears to be a substrate for ‘central inhibition’ in primates (Terasawa 2005). When GABA inhibition is removed or decreased, stimulatory input from glutamatergic neurons as well as norepinephrine and neuropeptide Y (NPY) neurons become active (Jarry *et al*. 1988, Terasawa & Fernandez 2001). In addition to neurotransmitters, more recently, glial cell regulation mechanisms have also been implicated in the activation of the GNRH neurons (Ojeda *et al*. 2003). The search for additional signals that herald the change in GNRH dynamics during puberty has continued in recent years with a genetic twist. These efforts, discussed in greater detail below, led to the discovery of the newest

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players in the regulation of GNRH secretion: kisspeptin and its receptor, KISS1R (previously known as GPR54).

KISS1R and its ligand kisspeptin

Although genetic studies ultimately placed KISS1R on the map as a key modulator of GNRH secretion, the biological life of KISS1R did not begin in reproduction. A member of the rhodopsin family of G-protein-coupled receptors, GPR54, was originally cloned in 1999 and was an orphan receptor until 2001 when its ligand was discovered to derive from kisspeptin (Kotani *et al*. 2001, Muir *et al*. 2001, Ohtaki *et al*. 2001). The longest peptide (kisspeptin 1 68–121) is known as 'metastin' but shorter C-terminal peptides share similar affinities and efficacies. The gene encoding kisspeptin, *KISS1*, has been localized to chromosome 1 and codes for a 145-amino acid protein that can be cleaved to form different length kisspeptins (West *et al*. 1998). C-terminal fragments have been shown to be potent KISS1R agonists (Kotani *et al*. 2001, Muir *et al*. 2001).

Interestingly, the original niche for kisspeptin was in cancer biology as it was isolated as a tumor metastasis suppressor gene in a human malignant melanoma cell line (Lee *et al*. 1996, Lee & Welch 1997*a*). Kisspeptin can suppress the metastatic potential of melanoma and breast cancer cell lines *in vivo* (Lee *et al*. 1996, Lee & Welch 1997*b*). More recently, the expression levels of *KISS1* have been found to be reduced in several, but not all, metastatic cancer specimens (Lee & Welch 1997*b*, Shirasaki *et al*. 2001, Sanchez-Carbayo *et al*. 2003, Dhar *et al*. 2004, Ikeguchi *et al*. 2004, Masui *et al*. 2004, Jiang *et al*. 2005, Ohta *et al*. 2005, Zohrabian *et al*. 2007).

Kisspeptin and pregnancy

While a relationship between kisspeptin's metastasis suppressor properties and the neuroendocrine role is not yet clear, high levels of kisspeptin have been discovered in the peripheral blood of pregnant women (Horikoshi *et al*. 2003). Moreover, prominent expression of KISS1R and kisspeptin has been demonstrated in human placenta at higher levels during the first trimester of pregnancy in comparison with the term placenta (Janneau *et al*. 2002). In fact, kisspeptin inhibits trophoblast invasion during placental formation (Bilban *et al*. 2004). Interestingly, decreased levels of both kisspeptin and *KISS1R* mRNA have been found in choriocarcinoma cells, thus suggesting an important link between kisspeptin action and trophoblast invasion during early pregnancy (Janneau *et al*. 2002).

Kisspeptin/KISS1R critical for puberty

The reproductive dimension of the kisspeptin/KISS1R system was revealed in late 2003, when two groups independently reported the presence of deletions and inactivating mutations of *KISS1R* in patients with idiopathic hypogonadotropic hypogonadism (IHH), a condition characterized by low sex steroids and gonadotropin levels (de Roux *et al*. 2003, Seminara *et al*. 2003). Along with the reporting of the loss-of-function mutations in humans, phenotypic characterization of mice with targeted deletion of *Kiss1r* was also described (Funes *et al*. 2003, Seminara *et al*. 2003). The *Kiss1r* knockout mice also displayed hypogonadotropic hypogonadism, demonstrating parallelism to the human disease model. In total, the linkage studies, *in vitro* assays, and mouse characterization established that KISS1R and its ligand play a fundamental role in the control of reproductive function in mammals.

Following these genetic discoveries, the pathway encompassed by kisspeptin and its receptor, KISS1R, has been the focus of intense study by investigators across several disciplines. The remainder of this review will explore the various models, particularly *in*

vivo, that have led to the remarkable exposition of the reproductive roles of kisspeptin and KISS1R.

Differential hypothalamic expression

Several studies have explored the distribution and temporal patterns of kisspeptin expression. Kisspeptin-expressing neurons are present in the arcuate nucleus (Arc), the periventricular nucleus (PeN), and the anteroventral periventricular nucleus (AVPV) in mice (Gottsch *et al*. 2004, Smith *et al*. 2005*a*, 2005*b*). Additional, but more subtle, expression is seen in the anterodorsal preoptic area and the bed nucleus of the stria terminalis.

Kisspeptin appears to undergo differential expression in distinct hypothalamic nuclei. Kisspeptin expression in the AVPV is sexually dimorphic, with much greater expression in females (Smith *et al*. 2005*b*). Gonadectomy increases the number of detectable *Kiss1* mRNA-expressing neurons as well as the content of *Kiss1* mRNA per cell in the Arc. Sex steroid replacement reduces *Kiss1* expression back to that of intact animals (Smith *et al*. 2005*a*, 2005*b*). These observations suggest that kisspeptin may modulate the negative feedback on GNRH secretion exerted by sex steroids. By contrast, gonadectomy decreases *Kiss1* expression in the AVPV and sex steroid replacement restores it. This suggests that kisspeptin participates in the positive feedback loop is seen in the female estrous cycle (Smith *et al*. 2005*a*, 2005*b*). Indeed, administration of kisspeptin-blocking antibodies to the brains of female rats blocks the mid-cycle LH surge (Adachi *et al*. 2007). Therefore, sex steroids appear to play a major role in kisspeptin expression, though many questions remain about how kisspeptin can stimulate transcription in one nucleus and repress it in another.

In contrast to the rodent, information on *KISS1* expression in the human is still quite limited. In the infundibular nucleus (corresponding to the Arc), post-menopausal woman have a higher number of kisspeptin-expressing neurons, an increased size of the neurons, and an increased quantity of kisspeptin mRNA per cell when compared with premenopausal woman (Rometo *et al*. 2007), confirming also in humans a possible role of this nucleus in the negative feedback on GNRH exerted by estrogens. These results are consistent with data from ovariectomized cynomolgus monkeys (Rometo *et al*. 2007). Comprehensive studies on the expression of kisspeptin across the human reproductive development have yet to be performed.

In mice and monkeys, *Kiss1* mRNA levels in the hypothalamus are low prior to sexual maturation but increase dramatically at the time of sexual development (Han *et al*. 2005, Shahab *et al*. 2005). Both male and female rats undergo considerable augmentation of hypothalamic *Kiss1* mRNA expression during the transition from juvenile to adult life (Navarro *et al*. 2004*a*). More specifically, *Kiss1* expression in the mouse AVPV (both number of neurons and kisspeptin content per cell) is greater in adult than in prepubertal animals (Han *et al*. 2005). In monkeys, *KISS1* mRNA increases in the hypothalamus across sexual maturation in both agonalad males and intact females. *KISS1R* mRNA increases in intact females as well, suggesting that increased expression of this pathway is the key to the timing of sexual development (Shahab *et al*. 2005).

In addition to increase in kisspeptin expression, kisspeptin tone appears to play a pivotal role in the onset and pacing of reproductive development. In sexually immature female rats, chronic administration of kisspeptin (6 days) advances the timing of sexual maturation as evidenced by precocious vaginal opening (Navarro *et al*. 2004*b*). In the human, mutations within the kisspeptin/KISS1R pathway establish varying degrees of kisspeptin ‘tone’ with clear effects on the timing and pace of pubertal development. As mentioned earlier, loss-of-function mutations in the gene encoding kisspeptin’s receptor, *KISS1R*, cause hypogonadotropic hypogonadism. Recently, a gain-of-function mutation in *KISS1R* has been

identified in a patient with central precocious puberty (Teles *et al*. 2008). Therefore, kisspeptin is an indisputable gatekeeper of pubertal function.

Impact of metabolic and environmental factors on kisspeptin expression

Fasting has a well-known inhibitory effect on gonadotropin secretion and ovulation. Paradoxically, *GNRH* gene expression at the hypothalamus is not reduced in the fasted state (Bergendahl *et al*. 1992). This suggests that modifications of the hypothalamic–pituitary–gonadal axis in fasting occur upstream from the GNRH synthesis pathways. Because of the considerable data pointing to kisspeptin as a critical gatekeeper for GNRH neuronal function, the interplay between energy stores, kisspeptin expression, and activation of the reproductive cascade has been explored by some investigators. Short-term fasting in male and female prepubertal rats simultaneously reduces *Kiss1* mRNA and increases *Kiss1r* mRNA levels compared with rats fed *ad libitum* (Castellano *et al*. 2005). Treatment with kisspeptin can restore indices of pubertal maturation in the majority of animals as well as reverse the suppressed gonadotropin and sex steroid levels. Leptin may be a link between the kisspeptin pathway and metabolism. The content of *Kiss1* mRNA in the Arc is significantly reduced in ob/ob compared with WT mice, and partially restored by leptin administration (Smith *et al*. 2006). Moreover, almost a half of *Kiss1* mRNA-expressing cells in the Arc express also leptin receptor mRNA, suggesting that kisspeptin is a key to the metabolic regulation of reproductive function (Smith *et al*. 2006).

Similar to undernutrition, uncontrolled diabetes in rodents is also characterized by decreased LH secretion (Jackson & Hutson 1984, Steger *et al*. 1989, Dong *et al*. 1991, Sexton & Jarow 1997). GNRH release is maintained in streptozotocin (STZ)-treated rats (Spindler-Vomachka & Johnson 1985, Clough *et al*. 1998), suggesting that the defect underlying the hypogonadotropism in these animals lies upstream from the GNRH neurons. Moreover, kisspeptin administration stimulates LH release in STZ-treated rats (Castellano *et al*. 2006). In turn, it has recently been shown that kisspeptin is able to reduce glucose-induced insulin secretion (but not basal insulin levels) in a dose-dependent manner, probably through a direct effect on pancreatic B cells, profiling a diabetogenic role of kisspeptin (Silvestre *et al*. 2008). In animals that breed seasonally, the length of the light–darkness cycle has a potent effect on reproductive function. In sheep, changes in the light–darkness cycle have been shown to modulate *KISS1* expression in the Arc. Specifically, the number of *KISS1* mRNA-expressing cells is reduced during seasonal anestrus and augmented at the onset of the breeding season (Smith *et al*. 2007). Administration of kisspeptin to seasonally acyclic ewes can induce ovulation (Caraty *et al*. 2007). Kisspeptin, therefore, appears to mediate the effects of multiple modulators of the reproductive endocrine axis including metabolism, energy stores, and light–darkness cycles.

Kisspeptin administration to intact animals: powerful stimulus to gonadotropin release

Kisspeptin peptides are powerful stimulators of gonadotropin secretion in several mammalian species, including rodents (Gottsch *et al*. 2004, Matsui *et al*. 2004, Navarro *et al*. 2004*a*, 2004*b*, 2005*a*, 2005*b*, Thompson *et al*. 2004, Messager *et al*. 2005), sheep (Smith *et al*. 2007), monkeys (Shahab *et al*. 2005, Plant *et al*. 2006), and even humans (Dhillo *et al*. 2005). The stimulatory effect of kisspeptin is extraordinary high, as intracerebral doses as low as 100/fmol evoke nearly maximal LH responses (Gottsch *et al*. 2004). The effects of kisspeptin on LH can be completely abrogated by a GNRH antagonist, demonstrating that it is acting through the GNRH receptor to stimulate LH release (i.e., hypothalamic effect; Gottsch *et al*. 2004, Shahab *et al*. 2005). Kisspeptin is unable to stimulate LH release when

given to *Kiss1r* knockout mice, suggesting that the stimulatory effects of this peptide are mediated only through this receptor (Messager *et al*. 2005).

Method of administration

In addition to timing and dose, the method of administration of kisspeptin may be equally critical in eliciting the gonadotropin response. Parallel to the classic experiments of Belchetz and Knobil with GNRH administration three decades ago (Belchetz *et al*. 1978), the mode of administration of kisspeptin (continuous versus intermittent) has profound effects on its ability to elicit gonadotropin secretion (Seminara *et al*. 2006). Continuous infusion of high-dose kisspeptin 112–121 (metastin 45–54) to juvenile, agonadal male rhesus monkeys initially stimulates LH release, but then abolishes the LH response (Seminara *et al*. 2006). The sustained suppression of LH levels during continuous exposure to kisspeptin is secondary to desensitization or down-regulation of *KISS1R*.

The finding has not only physiological but also therapeutic implications. In clinical practice, reversible suppression of the pituitary–gonadal axis is often a desired endpoint in the treatment of certain reproductive cancers, endometriosis, and infertility. The fact that continuous kisspeptin administration can also bring about the suppression of LH levels, suggests that it (or its analogues) might be novel therapeutic possibilities for the treatment of reproductive disorders in the future.

Return to genetics

In 2001, ~40% of probands with autosomal recessive normosmic hypogonadotropic hypogonadism (IHH) and 10–17% of sporadic cases were found to harbor mutations in the *GNRHR*, the gene encoding the GNRH receptor (Beranova *et al*. 2001, Bo-Abbas *et al*. 2003). Clearly, additional genes were awaiting discovery.

As briefly described earlier in 2003, groups independently identified KISS1R as a gatekeeper of puberty (de Roux *et al*. 2003, Seminara *et al*. 2003). de Roux *et al*. (2003) recruited a consanguineous family in which five out of eight children had IHH. Seminara *et al*. (2003) studied a large Saudi Arabian family in which three marriages between first cousins produced six affected and thirteen unaffected offspring. In both pedigrees, a genome-wide scan led to evidence for linkage on chromosome 19 and ultimately the discovery of mutations in *KISS1R*. Since 2003, other loss-of-function *KISS1R* mutations have been discovered and characterized (de Roux *et al*. 2003, Seminara *et al*. 2003, Lanfranco *et al*. 2005, Semple *et al*. 2005, Tenenbaum-Rakover *et al*. 2007). Mutations in *KISS1R* span the length of the receptor without a ‘hotspot’ (Fig. 1).

Although the number of *KISS1R* mutations reported in the literature is small, there are some unifying characteristics in the patients who harbor them. Anosmia, midline facial defects, and skeletal anomalies do not figure prominently. All individuals with homozygous or compound heterozygote mutations fail to undergo pubertal development, while heterozygous family members are devoid of obvious reproductive phenotypes. Patients with *KISS1R* mutations retain responsiveness to both exogenous pulsatile GNRH and gonadotropins (Seminara *et al*. 2003, Pallais *et al*. 2006). During 10-min blood sampling, low-amplitude LH pulses can still be detected in patients with *KISS1R* mutations (Seminara *et al*. 2003, Pallais *et al*. 2006). Therefore, loss-of-function mutations seem to reduce GNRH without interfering with the intrinsic GNRH pulse generator (de Roux *et al*. 2003, Seminara *et al*. 2003).

As with *GNRHR* mutations, the prevalence of *KISS1R* mutations is higher among familial than non-familial probands. However, mutations are much more common in *GNRHR* than in

KISS1R (Cerrato *et al*. 2006). Considering *GNRH* and *KISS1R* together, it is reasonable for patients with normosmic IHH undergo genetic screening.

If loss-of-function mutations in *KISS1R* cause IHH, could gain-of-function mutations cause central precocious puberty? Recently, a new *KISS1R* mutation (R385P) was identified in an 8-year-old adopted Brazilian female with precocious puberty (Teles *et al*. 2008). In *in vitro* studies, the mutated receptor was found to exhibit prolonged activation of second messenger signaling pathways compared with wild-type *KISS1R*.

Targeted deletion of Kiss1r and Kiss1

In general, both *Kiss1r*$^{-/-}$ and *Kiss1*$^{-/-}$ mice mirror their human counterparts with abnormal sexual development (Funes *et al*. 2003, Seminara *et al*. 2003, d'Anglemont de Tassigny *et al*. 2007, Lapatto *et al*. 2007). Female mutants have delayed vaginal opening, whereas mutant males have shorter anogenital distance. Mutant mice of both sexes exhibit small gonads, reduced levels of FSH and LH, and infertility. Despite these markers of hypogonadism, there are some interesting paradoxes in the mice. Both *Kiss1r*$^{-/-}$ and *Kiss1*$^{-/-}$ male knockouts demonstrate spermatogenesis although it is impaired (d'Anglemont de Tassigny *et al*. 2007, Lapatto *et al*. 2007). In addition, some female mutant mice exhibit partial sexual maturation, with about half of *Kiss*$^{-/-}$ females and a smaller proportion of *Kiss1r*$^{-/-}$ females demonstrating persistent vaginal cornification (Lapatto *et al*. 2007). Detailed studies of estrous cycling and sexual behavior will be required to fully understand the phenotypes of these animals.

In conclusion, the kisspeptin/KISS1R system has been demonstrated to have a crucial role in the initiation of sexual maturation across mammalian species and maintenance of the normal reproductive function. Further studies will continue to elucidate the richness and complexity underlying the biology of the pathway. In addition, understanding kisspeptin and KISS1R physiology may aid the development of new reproductive therapies.

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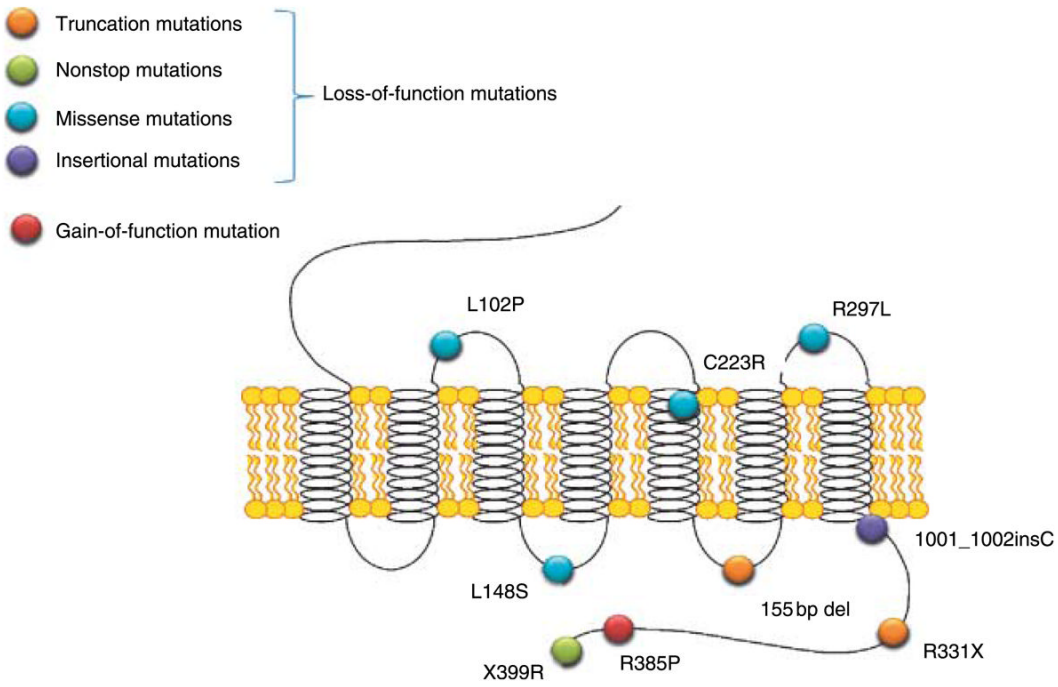

Figure 1.
The currently known mutations in the human *KISS1R* gene.