The role of kisspeptin signalling in the regulation of the
GnRH-gonadotrophin ovarian axis in mice

Rôle de la signalisation des kisspeptines dans la régulation de l’axe
GnRH-gonadotrophines ovaires chez la souris

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Résumé

Les kisspeptines correspondent à un ensemble de peptides codés par le gène KISS1 et nécessaires à l’activation centrale de l’axe hypothalamo-hypophyso-ovarien à la puberté. Les mutations affectant la signalisation des kisspeptines empêchent le développement pubertaire normal chez l’homme et la souris. Les mutations du récepteur KISS1 (GPR54) entraînent une infertilité et un hypogonadisme hypogonadotrope chez l’homme. L’incapacité des souris mutées, au niveau des gènes Gpr54 et KISS1 à ovuler, laisse penser que la signalisation par les kisspeptines est requise pour le pic préovulatoire de luteinizing hormone (LH). Par ailleurs, bien que les kisspeptines aient un rôle central important dans la régulation physiologique de l’ovaire, le profil d’expression de kiss1 et de Gpr54 suggère qu’elles pourraient aussi avoir des fonctions directes dans l’ovaire et le placenta.

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Mots clés : Kisspeptine ; GnRH ; Gonadotrophines ; Ovaires ; Souris

Abstract

Kisspeptins are a series of overlapping peptides encoded by the Kiss1 gene that are required for central activation of the hypothalamic-pituitary-ovarian axis at puberty. Mutations that interfere with kisspeptin signalling prevent normal pubertal development in humans and mice. Mutations in the kisspeptin receptor GPR54, cause infertility and hypogonadotropic hypogonadism in humans. The failure of the Gpr54 and Kiss1 mutant mice to ovulate has led to the suggestion that kisspeptin signalling may be required for the preovulatory luteinizing hormone (LH) surge. Although kisspeptin signalling has been shown to have an important central role in regulating the physiology of the ovary, the expression profile of Kiss1 and Gpr54 suggests that they may also have direct functions in the ovary and the placenta.

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Keywords: Kisspeptin; GnRH; Gonadotrophin; Ovary; Mice

1. Kisspeptin signalling is required for activation of the reproductive axis at puberty

Kisspeptins are a series of overlapping peptides encoded by the Kiss1 gene that are required for central activation of

the hypothalamic-pituitary-ovarian axis at puberty. The Kiss1 gene encodes a 145 amino acid protein that is processed into shorter amidated peptides of 54 (metastin or Kp54), 14 (Kp14), 13 (Kp13) or 10 (Kp10) amino acids [1–3]. Kisspeptin-expressing neurons are found in discrete regions of the hypothalamus including the arcuate (ARC) and the anterodcentral periventricular (AVPV) nuclei [4]. Kisspeptins signal through GPR54 (KISS1R), a G-protein coupled receptor, to stimulate gonadotrophin releasing hormone (GnRH) secre-
tion [5]. Consequently, kisspeptins stimulate gonadotrophin secretion in several species after systemic or central injection [4,6–9]. Kisspeptin injection can induce ovulation in prepubertal animals and activate GnRH neurons as judged by an increase in c-fos immunoreactivity [6,7]. Central administration of kisspeptin to immature female rats can induce precocious activation of the gonadotrophic axis, causing advanced vaginal opening, elevated uterus weight, and increased serum levels of LH and estrogen [10].

Mutations that interfere with kisspeptin signalling prevent normal pubertal development in humans and mice. Mutations in KISS1R cause infertility and hypogonadotropic hypogonadism in humans [11]. Similarly, transgenic mice with a disruption of the Gpr54 [11–14] or the Kiss1 [15,16] gene fail to undergo sexual maturation and show poor development of the gonads. Mutant mice are infertile with low gonadotrophic and sex steroid hormone levels [17]. Mutant females do not show normal estrous cycling or ovulation. The uterus are thread like and the ovaries significantly smaller than normal with no corpora lutea. Kiss1 and Gpr54 are not essential for ovulation, however, as we have shown that mutant mice can ovulate following stimulation with gonadotrophic hormones [11,15]. These data are consistent with a central defect in the mutant mice that results in a failure of GnRH/gonadotrophin secretion to stimulate ovarian function.

2. The role of kisspeptin signalling in the preovulatory LH surge

The failure of the Gpr54 and Kiss1 mutant mice to ovulate has led to the suggestion that kisspeptin signalling may be required for the preovulatory surge. Several lines of data support this hypothesis. Kiss1 is expressed in the AVPV region of the hypothalamus; an area known to regulate the pre-ovulatory LH surge in rodents. Kiss1 mRNA levels in the AVPV fluctuate during the estrous cycle with highest expression just before ovulation in rats [18]. Kiss1 expression in AVPV neurons is increased in response to estradiol treatment and Kiss1 neurons are activated as indicated by c-fos induction. Immuno-neuralization of kisspeptin in the preoptic area (POA) prevents the LH surge in rats [18]. Most significantly, Gpr54 or Kiss1 mutant mice cannot be induced to show an estrogen-primed LH surge [19].

3. The role of kisspeptin signalling in ovarian physiology and placentation

Although kisspeptin signalling has been shown to have an important central role in regulating the physiology of the ovary, the expression profile of Kiss1 and Gpr54 suggests that they may also have direct functions in the ovary and the placenta. Both Kiss1 and Gpr54 have been detected by RT-PCR in the rat ovary [20] and kisspeptin immunoreactivity has been found in the thecal layers of developing follicles, in the ovarian surface epithelium and in newly formed corpora lutea [21,22]. Kiss1 expression in the ovary is regulated by LH and fluctuates during the estrus cycle with highest expression at early proestrus [21]. Moderate kisspeptin is also found in regressing corpora lutea particularly in steroidogenic cells. Similarly, KISS1R immunoreactivity has been localized to the thecal layer of pre-ovulatory follicles and steroidogenic luteal cells of the corpus luteum. Kiss1 and Gpr54 expression increase in the ovaries of hamsters at the transition from non-breeding to breeding conditions [23]. We have found that mutant mice that have been induced to ovulate by injection of gonadotrophic hormones have lower progesterone levels than wild-type mice and we are investigating whether this represents an intrinsic defect in the corpus luteum.

In the placenta, Kiss1 is expressed by syncytiotrophoblast cells [24,25] which represent the cellular interface between the placenta and the maternal blood. In contrast, KISS1R expression is more extensive, being found in syncytiotrophoblast and cytotrophoblast cells [24]. Expression of KISS1R by the highly invasive cytotrophoblast cells has led to the suggestion that these proteins may regulate placental invasion but the birth of Gpr54 and Kiss1 mutant mice indicates that placentation can take place in the absence of kisspeptin signalling from the fetal part of the placenta. To investigate the effect that loss of both maternal and fetal kisspeptin signalling may have on placental function, we are restoring fertility to the mutant mice by hormone treatment and trying to establish pregnancy. Initial data indicate that pregnancy is not maintained in the mutant mice past day 7 of gestation even after progesterone treatment. We are investigating the causes of this failure to maintain pregnancy.

Conflict of interest

None.

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References


