Kiss/Kiss1r system in reproductive axis, interaction with NKB

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Kisspeptins form a family of related peptides codified by KISS1 gene located at chromosome 1q32.1 (1). Their biological actions are carried through specific receptor called KISS1R that belongs to G protein-coupled receptors rhodopsine-like family (2). Isolated mutations in these genes cause hypogonadotropic hypogonadism in humans, exposing the role of the system in reproductive function (3,4). In this sense, reproductive deficiencies in KISS1R and KISS1 knockout mices prove their role in maintenance of reproductive axis (5-8). Both humans and modified mice do not exist decreases of GnRH content at hypophysary level. These facts suggest that KISS1/KISS1R system regulate GnRH release at hypothalamic level (9). Two neuronal populations expressing kisspeptins have been identified at hypothalamus (10). One of them is present at arcuate nucleus (11) and, there, kisspeptin is co-located with neurokinin B and dynorphin, creating a neuron population called KND (12,13). The other one appears at anteroventricular paraventricular nucleus (14). Nevertheless, KISS1R is only expressed in gonadotropin-releasing hormone neurons (15). On the other hand, direct neuronal connections have been shown between arcuate nucleus and anteroventricular paraventricular neurons and gonadotropin-releasing homone neurons (16).

Kisspeptins are powerful agonists for releasing gonadotropins (17,18). Kisspeptin administration causes FSH and LH secretion in mice, rats, monkeys and humans, both males and females. LH release kinetic is faster than FSH release kinetic, but this one is longer in time (19-24). Normal gonadotropin release needs pulsatile content of kisspeptin, since chronic administration of kisspeptin induces a quick but short answer (25). Kisspeptin action in gonadotropin-releasing hormone induces a membrane depolarization that stimulates PLC-Ca2+ pathway causing changes in K+ and Na+ conductivity and subsequent GnRH release (21,26). GnRH release kisspeptin-dependent is abolished by GnRH antagonist (19,27). Gonadectomy produces an increase of kisspeptin expression at arquate nucleus level, inducing a rise of circulating FSH and LH. Female estradiol or male testosterone supplementation normalizes kisspeptin and gonadotropin levels. This fact displays a sexual hormone negative feedback on GnRH release at arquate nucleus level (14,28-31). In contrast, gonadectomy reduces kisspeptin expression at anteroventral and paraventricular nucleus, being reestablished after sexual homones supplementation, constituting a positive feedback in this neuronal population (14,28,32). This function is essential in female late follicular phase to trigger LH peak previous ovulation, when estradiol levels are high and progesterone is detectable in circulating blood (33). KISS1R antagonists prevent preovulatory LH peak (34). In this sense, the use of kisspeptins to trigger ovulation in IVF cycles has been reported with effective and safe results, especially in women with OHSS risk (35).

Furthermore, isolated mutations in coding genes of NKB and its specific receptor NK3R produce hypogonadotropic hypogonadism, with similar phenotypes as caused by KISS1 and KISS1R mutations (36). NKB belongs to a family of small peptides called tachykinins together with SP and NKA. Specific receptors of tackykinins are NK1R, NK2R and NK3R (37). As we know, NKB is present in KND neurons at hypothalamic arquate nucleus. NK3R also appears in this neuronal population (38-40). These neurons are highly interconnected, so NKB is probably released in the same neuronal population where is synthetized with a paracrine function that generates an increase in kisspeptin exocytosis that finally elevate GnRH secretion (41-44).

Direct effect of NKB administration over LH release is not clear because it could be under specific hormonal milieu control or specie-specific response (9). However, FSH is clearly not affected by NKB administration (45). Anyway, any possible effect of NKB over GnRH release is produced before KISS1R activation, as experiments in KISS1R knockouts mice demonstrate (46).

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