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Editorial

Kisspeptin system in female reproduction: A next-generation target in the manipulation of sex hormones

The discovery of the neuropeptide kisspeptin, originally derived from its antimetastatic property affecting malignant melanoma cells, as well as its role in reproductive function, was a milestone in the field of reproductive biology.[1,2] Conventionally, the capacity for reproductive activity in mammals involves coordinated communication between the hypothalamus, the anterior pituitary, and the gonads [the hypothalamic–pituitary–gonadal (HPG) axis]. This includes hypothalamic neuropeptides [gonadotropin-releasing hormone (GnRH), synthesized in GnRH neurons scattered throughout the preoptic area, as well as the organum vasculosum laminae terminalis, and releasing into the portal circulation in a pulsatile manner], gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secreted by pituitary gonadotroph cells], and sex steroid hormones (androgen secreted by theca cells, as well as estrogen secreted by granulosa cells and progesterone secreted by luteinizing theca and granulosa cells) secreted by the ovaries.[1] However, there have been significant advances in our understanding of the hierarchical pathways that control GnRH release, where it has been particularly noted that peptides and signaling pathways regulate GnRH neuronal activity. Evidence now indicates that kisspeptins, encoded by the *KISS1* gene and secreted by kisspeptin neurons, are critical regulators of sexual differentiation and maturation, as well as normal adult reproduction function in female mammals (menstrual cycles in women and estrous cycles in rodents).[3,4] Kisspeptin neurons are localized in the arcuate nucleus and the rostral periventricular nucleus of the third ventricle or the preoptic area. The latter releases kisspeptin to gonadotrophs (GnRH neurons) and is mediated by kisspeptin receptors (Kiss1r) that are highly expressed in GnRH neurons and in other areas of the brain, as well as in most endocrine tissues, including the pituitary gland, ovary, and placenta.[5]

The study by Luo et al[6] in this issue of the *Journal of the Chinese Medical Association* entitled, "Expression of kisspeptin/kiss1r system in developing hypothalamus of female rat and the possible effects on reproduction development and maintenance" evaluated correlations between activity and/or expression of the kisspeptin/kiss1r system in the hypothalamus of rats and development of rats from Day 7 of infancy to Day 63 of adult stage. The authors found that the coexpression pattern of the kisspeptin/kiss1r system and GnRH I in the ventromedial nucleus of the hypothalamus and around the ventral surface of the third ventricle in rats was time dependent, revealing the lowest expression levels occurring during the infant stage and higher expression levels during the adult age. Based on the obvious and significant time-dependent and progressive increase in coexpression of both the kisspeptin/kiss1r system and GnRH I, the authors concluded that the kisspeptin/kiss1r system may be mediated through GnRH neurons to activate and maintain reproductive function.[6] As a result,[6] this current issue reconfirmed the critical role of kisspeptin/kiss1r in the reproductive system. However, Luo et al's[6] paper did not provide additional information regarding the relationship between the initiation of ovulation cycles (or aging processes of the ovary) and activity of the kisspeptin/kiss1r system. Additionally, the authors also failed to discuss the expression patterns of kisspeptin neurons located in different areas, given that the two populations of kisspeptin neurons respond differently to estradiol feedback from the ovary through sexual dimorphism.[4] It was reported that kisspeptin neurons in the rostral periventricular nucleus of the third ventricle presented a marked sexual dimorphism, with more kisspeptin neurons in females compared to males, and represented the main drivers of preovulatory GnRH/LH surge.[4] By contrast, kisspeptin neurons in the arcuate nucleus are not sexually dimorphic.[4] Furthermore, GnRH neurons do not express estrogen receptor α, which is a primary estrogen target,[7,8] suggesting that estrogen acts as a regulator of GnRH secretion through an indirect mechanism. In fact, estrogen feedback to GnRH neurons is mediated by kisspeptin neurons, which display estrogen-dependent changes in kisspeptin expression.[4] Therefore, it is well known that the use of GnRH analogues to control HPG functions via stimulatory or inhibitory mechanisms of action[9,10] might also be reproducible by kisspeptin analogues, suggesting that Kiss1r agonists and antagonists might provide another option to control HPG functions.[11] Additionally, the kisspeptin/neurokinin B/dynorphin system in the arcuate nucleus has provided important clues to the neural mechanisms of GnRH pulse-generation systems.[12]

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A recent review by Matsui and Asami[11] summarized the available knowledge of both agonist and antagonist. Kisspeptin agonists more profoundly suppressed testosterone levels in rats and monkeys relative to natural kisspeptin, and Phase I clinical studies showed that subcutaneous infusion of kisspeptin analogues for 2 weeks in healthy male volunteers rapidly, but reversibly, reduced testosterone levels in a dose-dependent manner.[13] This effect might vary dramatically in normal healthy women, because twice-daily subcutaneous injection of kisspeptin analogues does not abolish menstrual cyclicity in healthy female volunteers.[14] This emerging new information suggested that additional physiological and pharmacological studies are necessary to deepen our understanding of the kisspeptin/kiss1r system to eventually provide novel therapeutic approaches similar to GnRH analogues, as we have previously reported.[15]

Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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