Kisspeptin in female reproduction

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Since 2003, kisspeptins (*KiSS*), the peptide products of the *KiSS* gene, binding to the G protein-coupled receptor 54 (*GPR54*, also called *KiSS1R*) are involved in various mechanisms regulating gonadotrope (gonadotrophin-releasing hormone [GnRH] neurons) axis as initiation of puberty, timing control of puberty and regulation of fertility in adulthood mediated by positive and negative feedback regulation on the hypothalamic-pituitary-gonadal (HPG) axis by gonadal steroids.[1–6] The *kisspeptin/KISS1R* system is complex partly because of neurons located in the arcuate nucleus (ARC), which also synthesize and secret many other neuromediators, such as neurokinin B and dynorphin to be involved in the control of HPG axis.[1,2,7] Specific mutations in *KiSS1R* gene cause either delayed/absent puberty or precocious puberty.[1–4] Although the main working place of the *KiSS/KiSS1R* system occurs in brain (central area), *KiSS* are also identified peripherally in the testes, ovaries, placenta, pancreas, and small bowel.[1,2] During pregnancy, *KiSS* are secreted from the placenta in large amounts and are responsible for the physiologic invasion of primary human trophoblast, and it is reported to reach a 7000-fold increase during the third trimester that observed in non-pregnant women.[2] In fact, based on the aforementioned observation, studies tried to evaluate the role of serum or plasma level of *KiSS* on the prediction of onset of preeclampsia or its correlated prenatal outcome, although the results are controversial,[8] since poor trophoblastic invasion during the initial placentation is believed as critical pathophysiology of developing preeclampsia.[9–11] Based on the above, we are happy to introduce the recent article entitled "Role of kisspeptin on cell proliferation and steroidogenesis in luteal cells in vitro and in vivo" published in this April issue of the *Journal of the Chinese Medical Association*.[12] This article is interesting and worthy of further discussion.

Similar to our editorial comment about the critical regulators of *KiSS/KiSS1R* system on sexual differentiation and maturation, as well as normal female adult reproductive function (menstrual cycles in women and estrous cycles in rodents),[5] we highlighted the importance of KiSS/KiSS1R system as a next-generation target site in the manipulation of reproductive function.

In the current article, Dr. Chiang's group conducted an *in vivo* observation of the cellular pattern of *KiSS/KiSS1R* in corpus luteal cells in female crossbred Taiwan native goats in the estrous cycle and found that the steroidogenic acute regulatory protein (*STAR*), cytochrome P450 cholesterol side-chain cleavage enzyme (*CYP11A1*), 3β-hydroxylated steroid dehydrogenase (*HSD3B*) and *KiSS/KiSS1R* were identified clearly in these corpus luteal cells.[12] A further *in vitro* study, the authors found the addition of *KiSS* in these corpus luteal cells could reduce the progesterone (P4) level, but, unexpectedly, increased cell proliferation.[12] The authors also found simultaneous down-regulation of *STAR*, *CYP11A1*, and *CYP11A1* in these corpus luteal cells after *KiSS* supplementation.[12] However, the results seemed to be against our understandings. In fact, we totally agree with simultaneous suppression of *STAR*, *CYP11A1*, *CYP11A1*, and P4. It makes sense. However, we are relatively confused to read that the proliferation of these luteal cells was increased.

Classically, corpus luteum composes two main cells, one is small luteal cells (SLCs) that are differentiated from the follicular theca cells and produce P4 in response to luteinizing hormone (LH), and the other one is granulosa cells luteinize to become large luteal cells (LLCs) that have a high rate of basal production of P4.[13] Since the formation and function of the corpus luteum rely on the appropriate proliferation and differentiation of both granulosa and theca cells, therefore, if any aspect of granulosa or theca cell luteinization is perturbed, then the resulting luteal cell populations (SLC, LLC, vascular, and immune cells) may be reduced and P4 production will compromise,

Against the authors' finding showing *KiSS* treatment led to the downregulation of P4 and increased proliferation of luteal cells in their study,[12] steroid hormone synthesis (P4 production) may be positively correlated with cell survivability. One study showed a dose- and time-dependent stimulatory effect of vascular endothelial growth factor (*VEGF*) on P4 synthesis and expression of steroidogenic enzymes; and moreover, *VEGF* treatment led to an increase in proliferating cell nuclear antigen (*PCNA*) expression and decrease in B-cell lymphoma 2 (BCL2)-associated X, apoptosis regulator (*BAX*) expression.[14] Although it is uncertain why the extra administration of different agents/cytokines/hormones will result in the diverse function of luteal cells, physiologic dose, or biphasic or triphasic effects or other undetermined reasons, such as paracrine, endocrine, and intracrine effects as an example,[15] may contribute to it. Therefore, we

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recommended that the study of role of *KiSS/KiSS1R* system on luteinization process had better be performed by extrapolating the impact that alterations in the theca and granulosa cell gene expression profiles and lineages could have on the formation and function of the corpus luteum.

In addition, in our previous comments,[5] we have shown that twice-daily subcutaneous injection of *KiSS* analogs more profoundly suppressed testosterone levels in rats and monkeys relative to natural *KiSS*, but in healthy male volunteers, *KiSS* analog reduced testosterone levels in a dose-dependent manner rapidly, although reversibly.[5] In addition, a similar treatment strategy is applied to normal healthy women, but no effect is found.[5] All suggest that *KiSS/KiSS1R* system in the regulation of reproductive function may be much more complex than we expected before. We are happy to learn much more studies focusing on the relatively brandy and new hormone system (*KiSS/KiSS1R* system), which is involved in reproduction, just like in this February issue and April issue of the *Journal of Chinese Medical Association*.[7,12]

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