บทบาทของแอนโดรเจนและอินฮิบินในการควบคุมพัฒนาการของฟองไข่และกระบวนการตกไข่

สุพัชญ์ สีนะวัฒน์
หน่วยชีววิทยาการเจริญพันธุ์ ภาควิชาสูติศาสตร์และนรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

Role of androgenic steroid and inhibin in control of follicular development and ovulation

Supat Sinawat
Reproductive Biology Unit, Department of Obstetrics and Gynecology
Faculty of Medicine, Khon Kaen University

Introduction

The granulosa and theca cells in developing follicles respond to endocrine stimulation of FSH and LH by producing steroid and nonsteroid regulatory factors. In turn, these regulartory factors affect paracrine and autocrine control of cell proliferation, differentiation, and migration in the maturing follicle. Androgenic steroid and inhibin produced by the theca and granulosa cells, respectively play important roles in modifying cellular responses of FSH and LH which are crucial for follicular development and ovulation.

Follicular development

Follicular growth to the stage of antrum formation (~ 0.25 mm diameter) is independent of gonadotropic stimulation[1]. However, follicular antrum formation and growth to the stage of preovulatory development require stimulation by FSH. FSH stimulates granulosa cell division, expression of several genes within granulosa cells such as cytochrome P450 aromatase, and P450 side chain cleavage enzymes, synthesis of LH receptors on maturing granulosa cells and production of regulatory proteins such as inhibin, activin and follistatin. [2-3]

At the early phase of each menstrual cycle, pituitary secretion of FSH increases due to withdrawal of negative feedback actions of estradiol, progesterone and inhibin produced by the previous corpus luteum.[4] This intercycle rise in plasma FSH level causes multiple antral follicles to enter preovulatory stages of development. Each follicle within this cohort has different FSH threshold required to initiate preovulatory development. During the midfollicular phase, follicle with greatest sensitivity to FSH or, in other word, has lowest FSH threshold, will begin to secrete estradiol and inhibin. Production of inhibin from immature granulosa cells of human is induced by FSH and augmented by androgenic steroids secreted from theca cells. Inhibin production becomes directly responsive to LH during advanced preovulatory development.[1, 5-6]

The theca cells of developing follicles produce diverse steroidal and nonsteroidal factors that are expected to influence granulosa cell functions in vivo. Androgen secreted from an LH-regulated theca cells is of paramount importance. Besides services as the obligatory precursor for estrogen synthesis, theca-derived androstenedione is metabolized by granulosa cells to testosterone and other androgens that are able to augment cytodifferentiative actions of FSH.[7] This regulatory effect appears to be mediated via specific androgen receptors and entails amplification of cAMP-mediated intracellular signaling. Aromatase activity and inhibin production are conspicious among the FSH-inducible granulosa cell functions promoted by androgen in vitro. Conversely, inhihin secreted from FSH-stimulated granulosa cells is able to promote LH-dependent thecal androgen synthesis in vitro. Thus, the potential exists for a reciprocal interaction between granulosa-derived inhibin and theca-derived androgen, which may give rise to development-related increases in estrogen synthesis.[8]

Both inhibin and estradiol secreted from dominant follicle have the potential to negatively regulate pituitary FSH release. This causes a progressive reduction in the circulating FSH level and thereby limits FSH-dependent development of other follicles with relatively high threshold requirements.[1, 9]

Androgen produced by theca interna and inhibin produced by granulosa cells of dominant follicle have potentials to act reciprocally and to amplify follicular responsiveness to gonadotropins. Thus, a single follicle become fully mature, protected against the fall in circulating FSH by its high responsiveness to both FSH and LH. Inhibin and androgen, therefore, may play crucial role in paracrine control of dominant follicle selection in monoovulatory species such as human [10-11]

Ovulation

LH receptors are constitutively expressed on theca cells and maturing granulosa cells of dominant follicle following stimulation by FSH. In response to the stimulation by LH, the dominant follicle secretes increased amount of androstenedione as well as estradiol.[1] Paracrine signaling by granulosa-secreted inhibin is thought to play role in selective enhancement of LH-responsive androgen synthesis that occurs in this follicle.[6] Theca-derived androgen, also, serves crucial role as precursor for estrogen production.[1, 8] After certain period of sustained high circulating levels of estradiol produced by preovulatory follicle is achieved, LH surge and subsequently ovulation occur.

After ovulation, progesterone, estrogen and inhibin secreted by the corpus luteum collectively exert negative feedback regulation of pituitary FSH secretion, thereby inhibiting preovulatory follicular development. Luteal phase plasma levels of progesterone, estradiol and inhibin rise to a maximum in the mid-luteal phase.[1-2, 12] If conception does not occur, corpus luteum will undergo atresia. Plasma concentrations of estrogen, progesterone and inhibin, thus, decrease due to luteal regression. This results in withdrawal of negative feedback effect to secretion of pituitary FSH.[1, 13] The new ovarian cycle stimulated by the rising of FSH, thus, occurs.

Summarized roles of theca-derived androgen:

1. Androgen serves as obligatory precursor for estrogen synthesis and it augments FSH-induction of aromatase activity of granulosa cells via an androgen-receptor regulated mechanism.

2. Androgen potentiation of steroidogenic enzyme induction during FSH-stimulated granulosa cell differentiation may involve a suppression of cAMP catabolism exerted by way of androgen-receptor system.

3. Androgen has the potential to modulate locally cytodifferentiative action of FSH on granulosa cells.

4. Androgen plays role in modulating the inhibin production from FSH-stimulated granulosa cells in vitro.

Summarized roles of granulosa-derived inhibin

1. Inhibin production increases coordinately with steroidogenesis during preovulatory follicular development in vivo.

2. FSH induces inhibin production in immature granulosa cells and inhibin becomes responsive to LH during advanced preovulatory develpoment.

3. Inhibin is unable to directly stimulate androgen synthesis but it potently enhances LH-responsive androgen synthesis in theca cells in vitro, implying an action, at a level involving P450 c 17. Inhibin may, therefore participate in a paracrine mechanism that locally amplifies androgen synthesis in the preovulatory follicle.

4. Inhibin plays significant paracrine effect in the regulation of estrogen synthesis by enhancing the theca-derived androgen production, hence, increases the aromatase precursor for estrogen production.

5. Inhibin, in addition to estrogen, plays important role in the selection process of dominant follicle. This results in monoovulation in particular species such as human.

Conclusion

In each menstrual cycle, a cohort of approximately 12-15 follicles are recruited to further develop to the stage of antral follicles. In human, however, only one dominant follicle is selected from this cohort to further develop to the pre-ovulatory phase. Development of these follicles as well as ovulatory process are complex mechanisms requiring the multi-steps control from several factors. Androgenic steroid and inhibin are among the examples of the paracine controls which exist within the ovary. Further research in this aspect will provide us more precise information about how human ovary actually works to successfully achieve mono-ovulation.

References

1. Zeleznik AJ, Hillier SG. The Ovary: Endocrine function. In: Hillier SG, Kitchener HC, Neilson JP, eds. Scientific Essentials of Reproductive Medicine. London: WB Saunders,1996:133-46.
2. Hillier SG. Hormonal control of folliculogenesis and luteinization. In: Findlay JK, ed. Molecular Biology of the female Reproductive System. London: Academic Press, 1994: 1-37.
3. Richards JS. Hormonal control of gene expression in the ovary. Endocr Rev 1994;15:725-51.
4. Le Nestour E, Marraoui J, Lahlou N, Rogers M. Role of estradiol in the rise in the follicle stimulating hormone levels during the luteral-follicular transition. J Clin Endocrinol Metab 1993;77:439-42.
5. Brown JB. Pituitary control of ovarian function- concepts derived from gonadotropin therapy. Aust NZ J Obstet Gynaecol 1978;18:46-54.
6. Findlay JK. An update on the roles of inhibin, activin and follistatin as local regulators of folliculogenesis. Biol Reprod 1993;48:15-23.
7. Magoffin DA, Erickson GF. Control systems of theca-interstitial cells. In; Findlay JK, ed. Molecular Biology of the Female Reproductive System. London: Academic press, 1994:39-66.

8. Erickson GF, Magoffin DA, Dyer CA, Hofeditz C. The ovarian androgen producing cells : a review of structure/ function relationships. Endocr Res 1985;6:371-99.
9. Hillier SG. Control of immunoreactive inhibin production by human granulosa cells. Clin Endocrinol 1991;35:71-8.
10. Hillier SG. Paracrine control of follicular estrogen synthesis. Semin Reprod Endocrinol 1991;9:332-40.
11. Smyth CD, Miro F, Howles CM, Hilier SG. Ovarian theca/ interstitial androgen synthesis is enhanced by a follicular-stimulating hormone-stimulated mechanism. Endocrinology 1993;133:1532-8.
12. Braden TD, Belfiore CJ. Hormonal control of luteal function. In : Findlay JK, ed. Molecular biology of the Female reproductive System. London: Academic Press, 1994:259-87.
13. Fisch B, Margara Ma. Cellular basis of luteal steroidogenesis in the human ovary. J Endocrinol 1989; 122:303-11.