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2009-05-20

The Two Cell Model of the Ovary

Since everything affects everything else, there are many possible places to start, but let's look at the ovary first. Falck first proposed the two-cell system in 1959, describing the interactions between the Granulosa and Theca cells.

Three definitions of hormone control mechanisms:
Paracrine control – local diffusion of a hormone from one cell to another
Autocrine control – intracellular control of one cell to another
Intracrine control – unsecreted substances that bind to intracellular receptors and work within a single cell

The Paracrine relationship from Theca to Granulosa cells:
At the start of the menstrual cycle, hormone levels are at their lowest level of the month. Granulosa cells already have some FSH receptors. Pituitary production of FSH induces further production of FSH receptors within the Granulosa cells. It is a positive feedback circuit and results in increasing Granulosa cell sensitivity to FSH. The Theca cells respond mostly to **LH** production by producing the androgens, **testosterone and androstenedione**. These two androgens diffuse out of the Theca cells and into the neighboring Granulosa cells. The Theca cells also make **IGF II** (Insulin Like Growth Factor II). It enhances LH stimulated production of androgens in the Theca cells. It also diffuses out into the Granulosa cells, stimulating **FSH** mediated **aromatization** of the androgens into estrogens. **Testosterone is changed into Estradiol and Androstenedione is aromatized into Estrone.**

Important in overeating America!
Although the Theca cells make mostly IGF-II, both IGF-I and IGF-II act by attaching to the **Type I- IGF receptor**. The importance of this will be stressed again when we deal with PCOS and **excess insulin states** in general. High Insulin levels can be caused by **insulin resistance** or any high insulin state, including excess **sugar and carbohydrate consumption**. Insulin attaches to and reacts with IGF-I receptors. Excess insulin can result in **Theca overproduction of androgens**. The Granulosa cell then change these excess androgens into estrogens, **resulting in estrogen excess**. Therefore, **excess insulin results in a high estrogen state**.

In the Granulosa cell, in response to FSH, Inhibin and Activin are produced. Inhibin enhances LH stimulation of androgen synthesis in the Theca cell whereas Activin suppresses androgen synthesis. These two proteins modify expression of the P450c17 enzyme system.
Prior to ovulation: Granulosa cells aromatize Theca produced androgens, turning them into estrogen.
This is an **FSH mediated activity**.
After ovulation: Granulosa cells secrete Progesterone and estrogen directly into the bloodstream:
This is an **LH mediated activity**.

Actually a three-cell system:
In the ovary, it is really a three-cell system; growing follicles are required. **It is only in the presence of growing follicles, and one dominant follicle in particular, that Inhibin-B is produced.** Granulosa cell production of Inhibin-B inhibits pituitary release of FSH and stimulates the release of LH. Rising estrogens, in a positive feedback loop, stimulate increases in FSH production and thereby, further increase in estrogen production. Inhibin-B puts the brakes on this runaway estrogen production. **Inhibin B production sets the stage for the LH surge that results in ovulation and Progesterone production by inhibiting FSH output and stimulating LH production.**

As women age: (This is the key to Dr. John Lee's peri-menopause progesterone therapy)
As women age, the number and health of follicles declines. This causes a decline in Inhibin-B production. **It is the decline in Inhibin-B production, and not the decline in estrogen production, that results in the rise in FSH in the peri-menopausal years.** There are many women with elevated FSH who have average, elevated or even very high levels of estradiol and estrone. Unless a healthy egg is released following ovulation at mid-cycle, no progesterone will be produced or released into the blood stream. As estrogen rises, so does LH. **Progesterone's effects on the brain and hypothalamus bring LH back down for the next cycle.** Without this resetting of the system, LH will remain elevated.

The PCOS like state of the peri-menopause: (A positive feedback loop)
Without quality follicles, there is **reduction in Inhibin-B** production and little or **no progesterone** produced. This results in **elevated FSH** but an **even higher LH**. Androgen and estrogen production are high but no progesterone is produced. Progesterone is required to lower LH and re-set the cycle. The elevated intra-ovarian androgens further inhibit ovulation. All this results in **Estrogen Dominance Syndrome**. The over stimulated endometrium begins to **bleed irregularly and heavily**. The patient craves carbohydrates and deposits intra-abdominal fat. Increasing abdominal fat causes insulin resistance. Insulin resistance **raises insulin** output. The excess insulin hits the IGF-I receptors in the theca cells stimulating excess testosterone and androstenedione production. The high FSH present stimulates the Granulosa cells to convert these excess androgens into estrogens. All this results in excess estrogen production. In addition, the **action of insulin on both insulin and IGF-I receptors in endometrial and breast tissue stimulates proliferation of these tissues**. This causes endometrial and breast hyperplasia leading to excess uterine bleeding and breast proliferation and probably increases both **endometrial and breast cancer risks**. It is not a pretty picture.

By simply replacing Progesterone and encouraging a low carbohydrate, reduced calorie diet, many of these problems subside or at least are reduced.

The Complexity of Control:
1. Within and outside of the ovary, the rate of aromatization of androgens to estrogens in influenced by: Cytokines, cyclic nucleotides, gonadotropins, glucocorticoids, and various growth factors.
2. Inhibitory agents of FSH include epidermal growth factor, fibroblast growth factor and GNRH like protein.
3. Inhibin enhances LH stimulation of androgen production,
4. Activin inhibits androgen synthesis.
5. FSH stimulates its own receptor production and LH receptor production.
6. SHBG (Sex Hormone Binding Globulin) levels are increased by: Hyperthyroidism, pregnancy, and estrogen.
6. SHBG levels are decreased by: corticosteroids, androgens, progesterone, growth hormone, insulin, IGF-I, weight gain and insulin resistance. Robert P. Goldman, M.D.