

BIOSINTESIS DAN MEKANISME KERJA HORMON REPRODUKSI WANITA

Kuliah 3

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Ovarian Sex Hormones

■ Types of ovarian sex hormones:

1. Estrogens

The most important of estrogens is **estradiol**

2. Progestins

The most important of progestins is **progesterone**

■ Production:

- > Non-pregnant: by
 - ovaries
 - adrenal cortices
- > Pregnancy: by
 - ovaries
 - placenta
 - adrenal cortices

Ovarian Sex Hormones.....

■ **Transport to target organ:**

- > Loosely bound with plasma albumin
- > More tightly bound with a beta globulin: sex hormone-binding globulin
 - specific estrogen-binding globulin
 - specific progesterone-binding globulin

■ **Mechanism of action:**

- > Location of receptors:
 - Cell interior
- > Signal transduction mechanism:
 - Receptors directly alter gene transcription
- > Only free hormone can diffuse across capillary walls and encounter its target cells

ESTROGENS

Types of Estrogens

■ **Beta-estradiol (17 β -estradiol):**

- major estrogen
- synthesized by ovaries
- strength: 12x estrone and 80x estriol

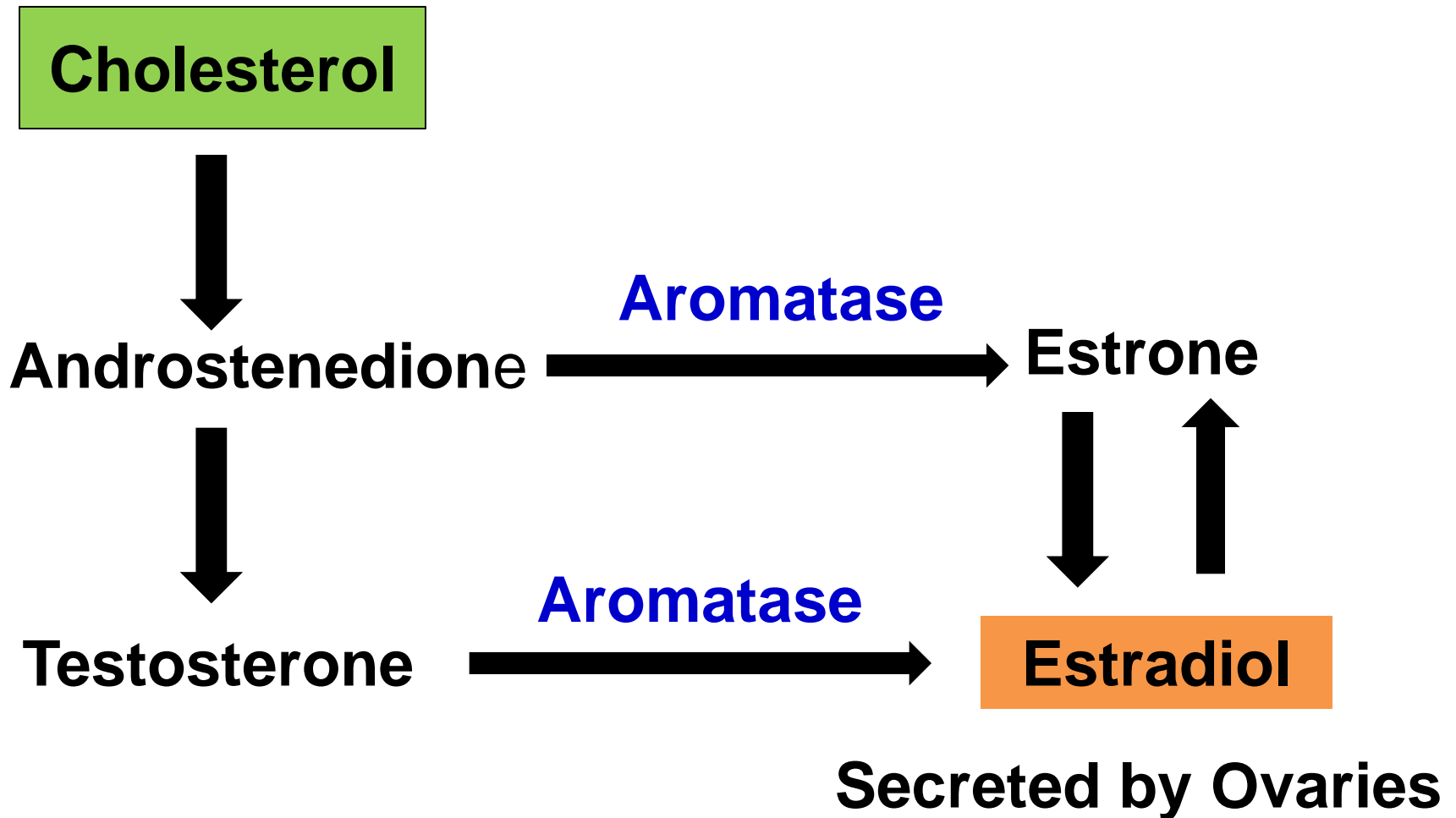
● **Estrone**

- by adrenal cortices, ovaries, and some other tissues

● **Estriol**

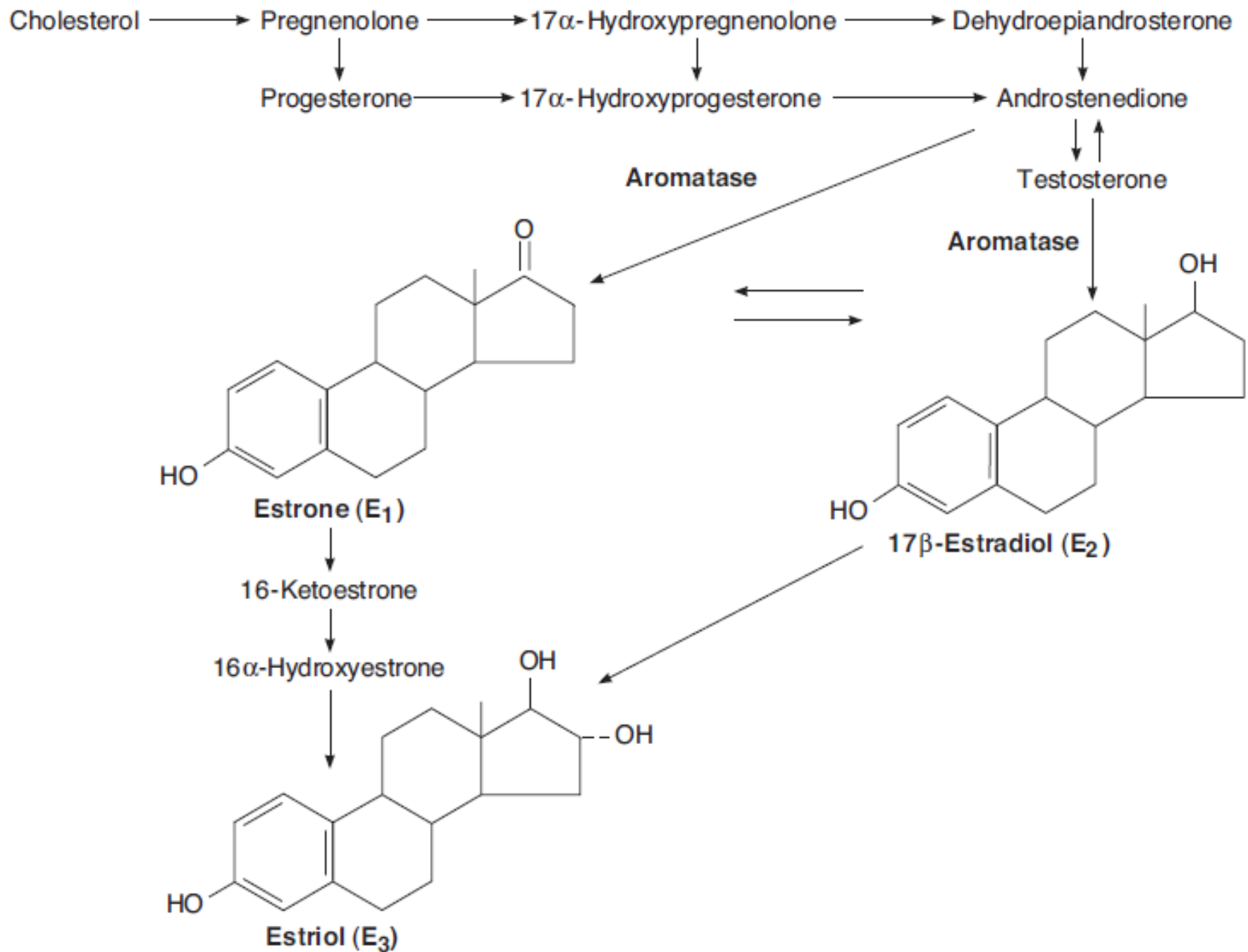
- oxidative product from estradiol and estrone
- by liver

Synthesis



Synthesis.....

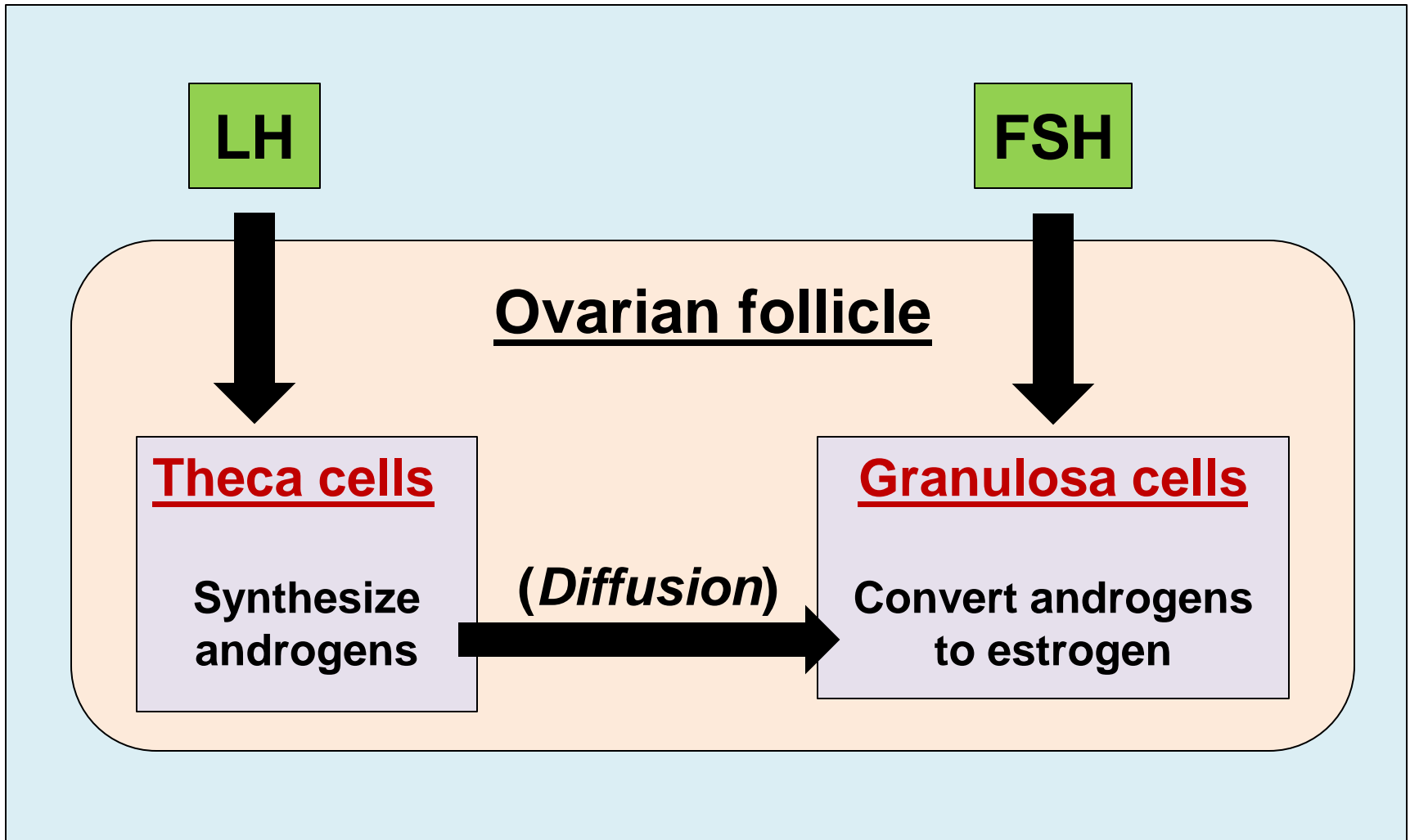
- The naturally estrogens (17β -estradiol, estrone, and estradiol) are C18 steroids
- The biosynthesis of estrogens depends on the enzyme aromatase (CYP19), which converts testosterone to estradiol and androstenedione to estrone
- The reaction of converting androstenedione to estrone also occurs in:
 - fat
 - liver
 - muscle
 - brain



Synthesis by Ovaries

- **Estrogen is synthesized and released into blood**
 - **during follicular phase mainly by granulosa cells**
 - **after ovulation by corpus luteum**
 - **during pregnancy by placenta**
- **Granulosa cells require help to produce estrogen because they are deficient in the enzymes required to produce androgens that are the precursors of estrogen**
- **They are aided by theca cells**
- **Requires interplay of both types of follicle cells and both pituitary gonadotropins (FSH and LH)**

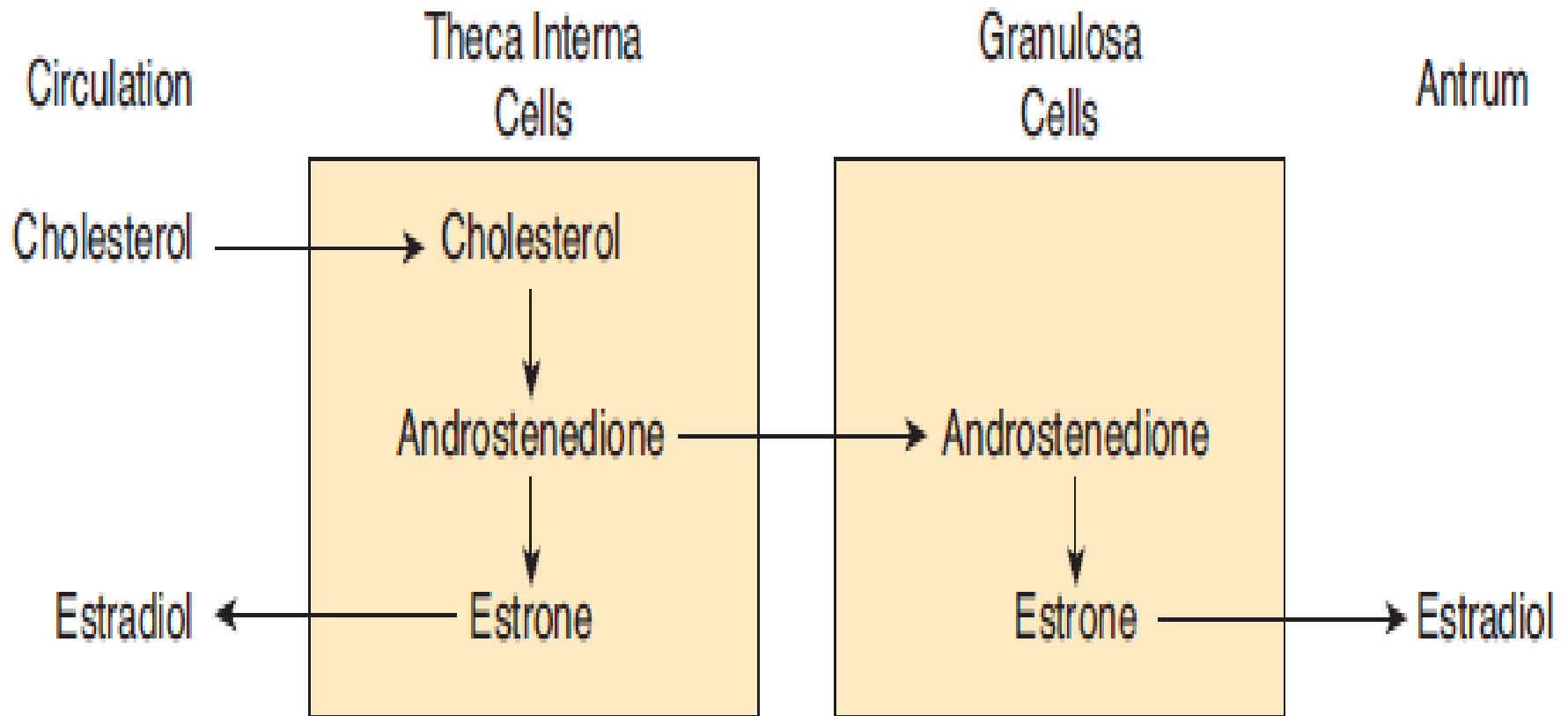
Synthesis by Ovaries.....



Synthesis by Ovaries.....

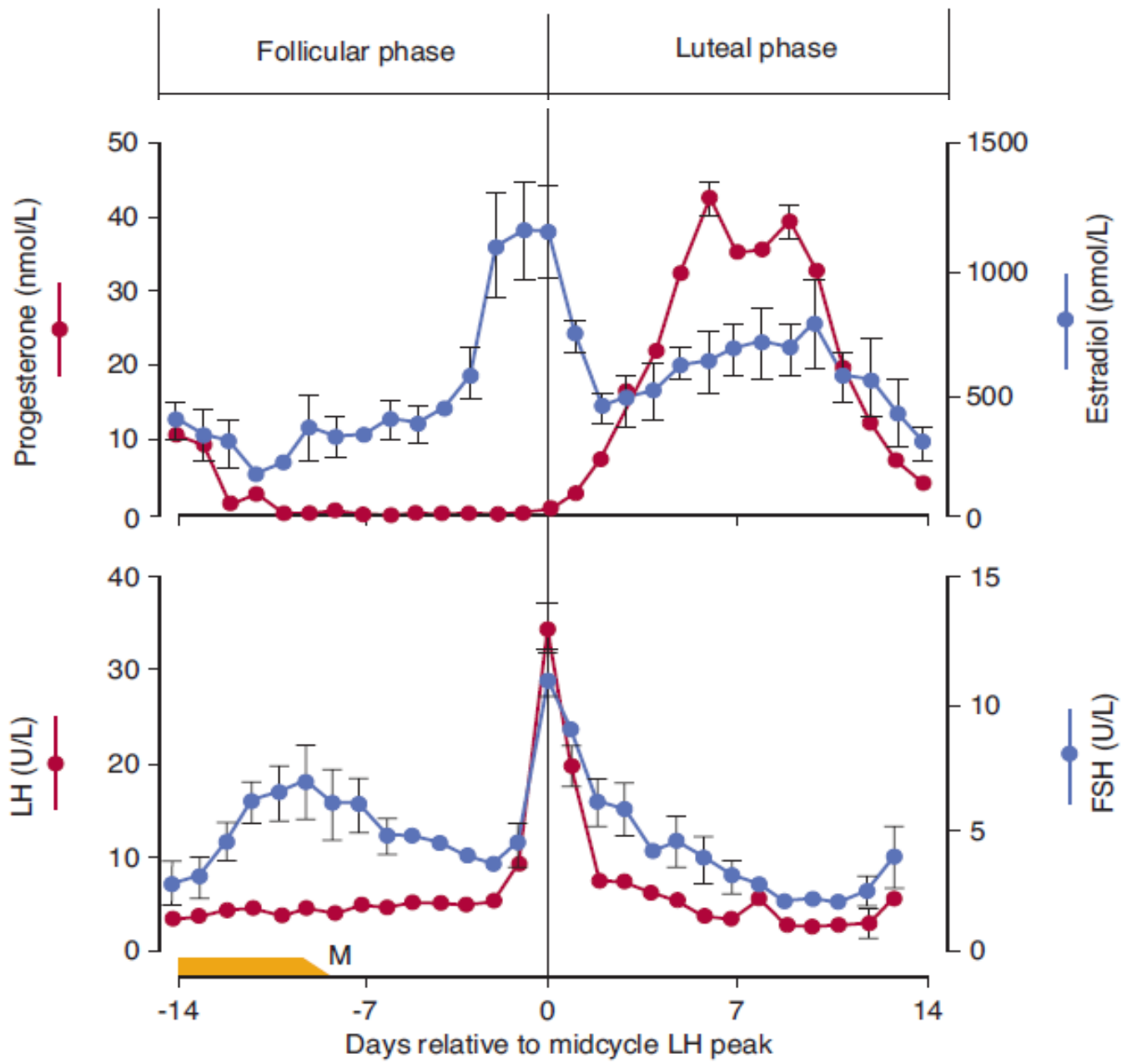
- Theca interna cells have many LH receptors
- LH acts via cAMP to increase conversion of cholesterol to androstenedione
- Theca interna cells supply androstenedione to granulosa cells
- Estradiol produced by granulosa cells when provided with androgen and secreted into follicular fluid
- Granulosa cells have many FSH receptors
- FSH facilitates the secretion of estradiol by acting via cAMP to increase aromatase activity
- Mature granulosa cells also require LH receptors

Synthesis by Ovaries.....



Secretion

- Concentration of estradiol in plasma during menstrual cycle is depend on menstrual phase
- Almost of this estrogen comes from ovary
- Two peaks of secretion occur: one just before ovulation and one during the midluteal phase
- Estradiol secretion rate is:
 - 36 $\mu\text{g}/\text{d}$ in the early follicular phase
 - 380 $\mu\text{g}/\text{d}$ just before ovulation
 - 250 $\mu\text{g}/\text{d}$ during midluteal phase
- After menopause estrogen secretion declines to low levels



Transport and Metabolism

- **Circulating estradiol: 2% is free, 60% is bound to albumin and 38% is bound to sex hormone-binding globulin /gonadal steroid-binding globulin (specific estrogen-binding globulin)**
- **Metabolism by liver:**
 - **conjugated → glucoronide and sulfate**
 - **excreted:**
 - **most in urine**
 - **in the bile (1/5) → enterohepatic circulation**
 - **estradiol & estrone → estriol (weak - impotent)**
 - **diminished liver function → hyperestrinism**

Distribution of gonadal steroids and cortisol in plasma

Steroid	% Free	% Bound to		
		CBG	GBG	Albumin
Testosterone	2	0	65	33
Androstenedione	7	0	8	85
Estradiol	2	0	38	60
Progesterone	2	18	0	80
Cortisol	4	90	0	6

CBG, corticosteroid-binding globulin; GBG, gonadal steroid-binding globulin.

Effects of Estrogen

- **3 Basic mechanisms of estrogen's effects on target organs/ cells**
 - **Promote proliferation and growth specific cell**
 - **Development of primary sex characteristic**
 - **Development of most secondary sex characteristics**
- **Non reproductive effects**
 - **Promotes fat deposition**
 - **Increases bone density**
 - **Closes epiphyseal plates**

Effects of Estrogen.....

On Sex-specific tissues

- Essential for egg maturation and release
- Stimulates growth and maintenance of entire female reproductive tract
- Stimulates granulosa cell proliferation which lead to follicle maturation
- Thins cervical mucus to permit sperm penetration
- Enhances transport of sperm by stimulating upward contractions of uterus and oviduct
- Stimulates growth of endometrium and myometrium

Effects of Estrogen.....

- **Induces synthesis of endometrial progesterone receptors**
- **Triggers onset of parturition by increasing uterine responsiveness to oxytocin during late gestation through a twofold effect by**
 - **inducing synthesis of myometrial oxytocin receptors**
 - **increasing myometrial gap junctions so that uterus can contract as a coordinated unit in response to oxytocin**

Effects of Estrogen.....

Other reproductive effects

- Promotes development of secondary sexual characteristics
- Controls GnRH and gonadotropin secretion:
 - Low levels: inhibit secretion
 - High levels responsible for triggering LH surge
- Stimulates duct development in breasts during gestation
- Inhibits milk secreting action of prolactin during gestation

Effects of Estrogen After Puberty

■ On uterus & external sex organ:

- Increase the size
- External genitalia enlarge with deposition of fat
- Change vaginal epithelium from cuboidal → stratified
- Endometrium changes:
 - > proliferation of the stroma
 - > greatly increased development of endometrial glands

■ On Fallopian tube:

- Proliferation of glandular tissue
- Increase the number of ciliated epithelial cell
- Enhance the activity of the cilia

Effects of Estrogen After Puberty....

■ On breast:

- Development of the stromal tissue
- Growth of an extensive ductile system
- Deposition of fat
- Develop lobules and alveoli (initiate growth)
- Characteristic growth and external appearance of the mature female breast

■ On metabolism:

- Increase metabolic rate (1/3 of testosterone)

■ On electrolyte balance: Na retention

- Slight and rarely significance, except in pregnancy

Effects of Estrogen After Puberty.....

■ On protein deposition:

- Slight increase in total body protein

■ On fat deposition:

- Increase quantities of fat in subcutaneous tissue → decreased specific gravity → flotation in water

■ On skin:

- Develop texture which is soft and smooth
- Thicker than children and more vascular
- Increase secretion of axillary sweat gland → acne (by adrenal androgen)

■ On hair distribution:

- No greatly effect (opposite to testosterone)

Effects of Estrogen After Puberty.....

■ On skeleton:

- Increase osteoblastic activity → growth
- Early uniting of the epiphyses with the shafts of long bone (stronger than testosterone)

Osteoporosis caused by estrogen deficiency:

- Diminished osteoblastic activity
- Decreased bone matrix
- Decreased deposition of Ca & Phosphate

■ On central nervous system

- Increase libido in humans and estrous behavior in animals by direct effect on neurons in hypothalamus
- Increase proliferation of dendrites on neurons in rats

Mechanism of Action

■ Intracellular function:

- circulate in blood only a few minutes → target cells
- combine with receptor protein in cytoplasm



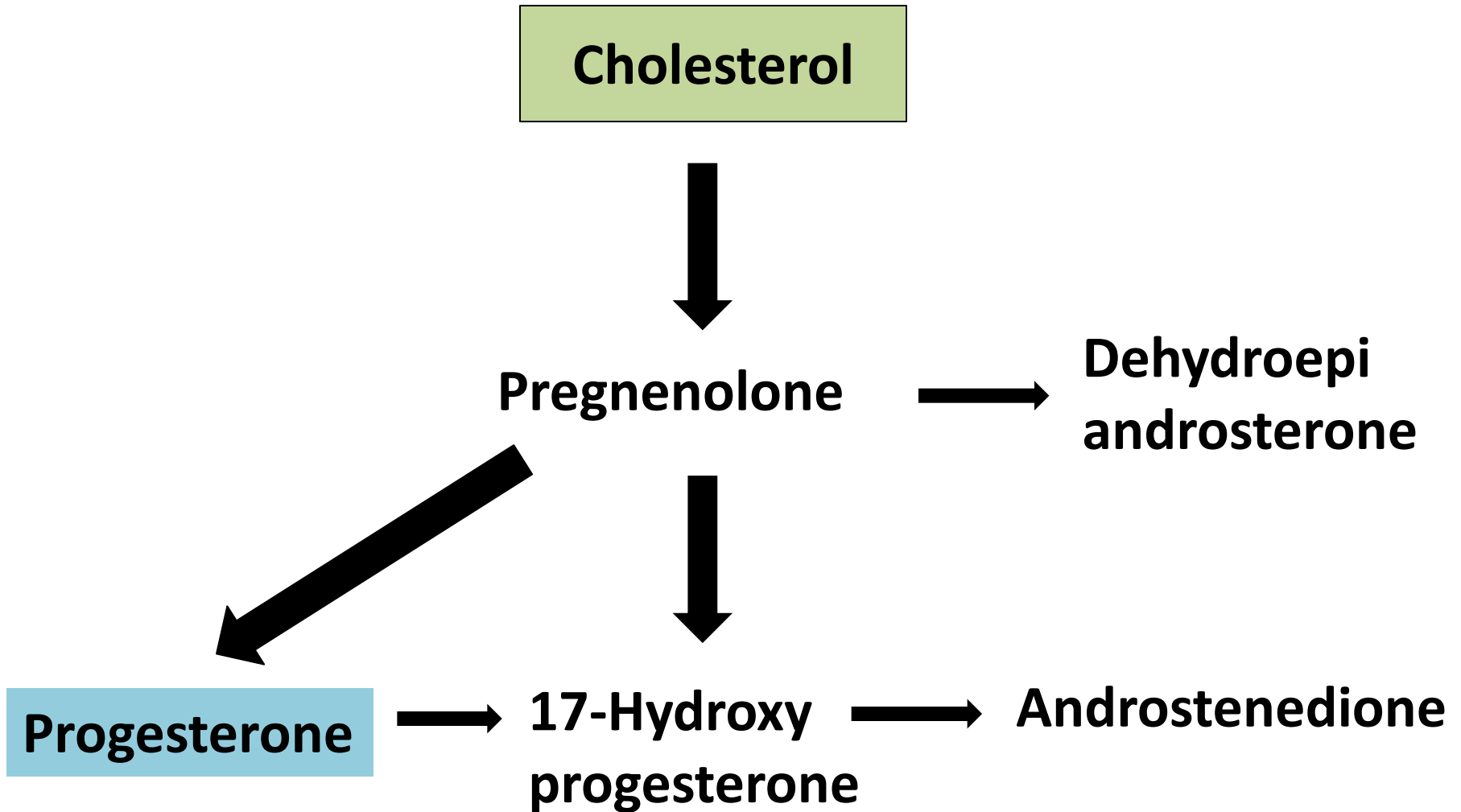
- activate specific portions of chromosomal DNA



- initiate transcription process → DNA – RNA →
 - > division of cell
 - > protein formation → in a few specific target organs

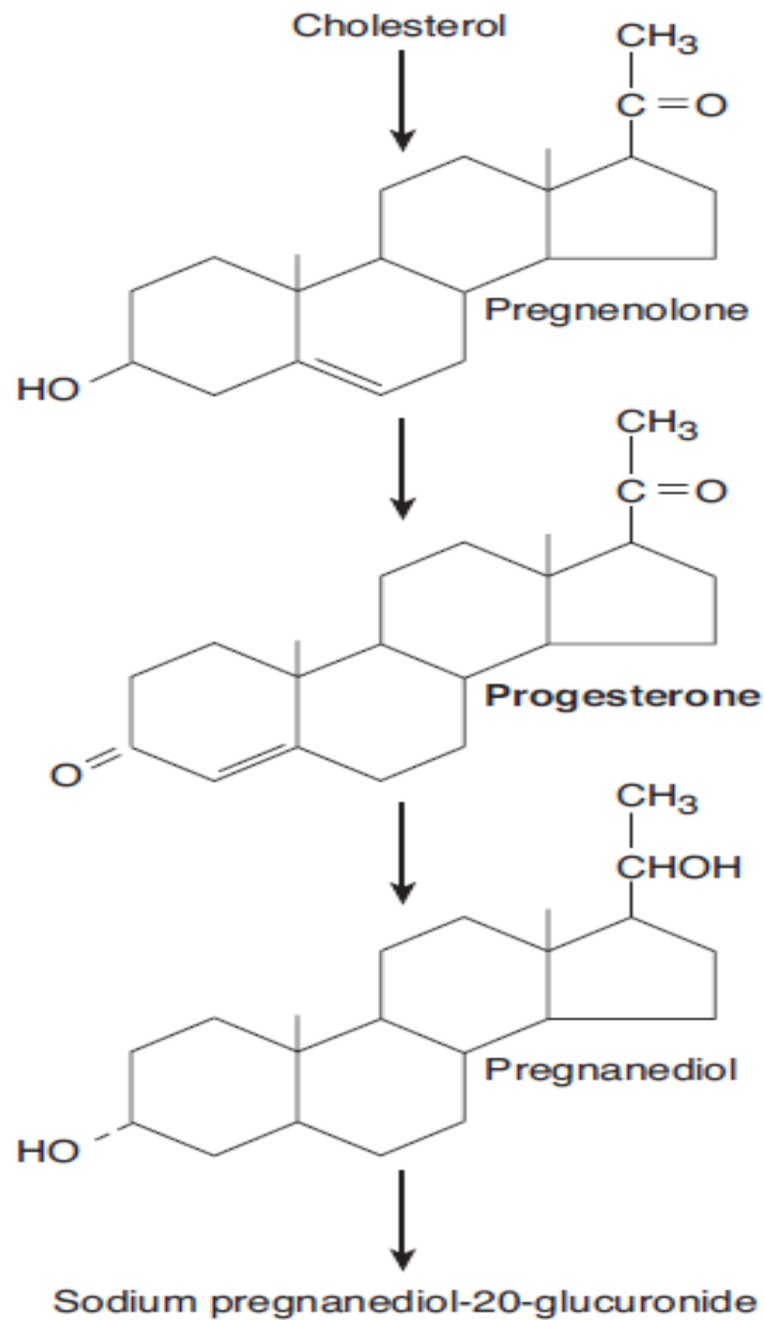
PROGESTIN

Synthesis



Synthesis

- **The most important type of progestin is progesterone**
- **Progesterone is C21 steroid**
- **Progesterone is synthesized and released into blood**
 - > **by ovaries:**
 - **major source is CL (after ovulation)**
 - **In very small amounts by granulosa and theca cells just before ovulation**
 - **placenta**
 - > **in small amount by cortex adrenal**



Secretion

- Concentration of progesterone in plasma during menstrual cycle is depend on menstrual phase
- Progesterone secretion rate is 0.9 ng/ml during the follicular phase, and late in follicular phase, progesterone secretion begins to increase
- During luteal phase, corpus luteum produces large quantities → plasma concentration markedly increased to a peak value of approximately 18 ng/ml
- Stimulating effect of LH is due to activation of adenylyl cyclase and involves subsequent step that is dependent on protein synthesis

Transport and Metabolism

- **Circulating progesterone: 2% is free, 80% is bound to albumin and 18% is bound to sex hormone-binding globulin /corticosteroid-binding globulin (specific progesterone-binding globulin)**
- **Progesterone has a short half-life**
- **Converted in liver to pregnanediol, which is conjugated to glucuronic acid**
- **Excreted in the urine**

Effects of Progesterone

- **Final preparation of the uterus for pregnancy**
 - Prepares a suitable environment of a developing embryo/ fetus
 - Promotes formation of a thick mucus plug in cervical canal
 - Inhibits uterine contractions during gestation
- **Final preparation of the breast for lactation**
 - Stimulates alveolar development in breasts during gestation
 - Inhibits milk-secreting action of prolactin during gestation
- **Inhibits hypothalamic GnRH and gonadotropin secretion**

Effects of Progesterone After Puberty

■ On uterus:

- promote secretory change during the latter half of cycle → preparing for implantation
- decrease frequency and intensity of uterine contraction → prevent expulsion of implanted ovum

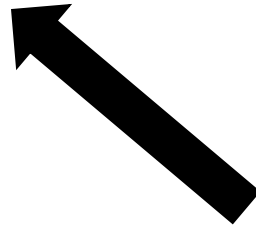
■ On Fallopian tube:

- promote secretory change → nutrition for fertilized ovum

Effects of Progesterone After Puberty.....

■ On breast:

- Development of lobules and alveoli
- Proliferate, enlarge, to become secretory of alveolar cells
- Cause breast swell



development in
lobules and alveoli

Increase fluid in
subcutaneous tissue

Effects of Progesterone After Puberty.....

■ On electrolyte balance:

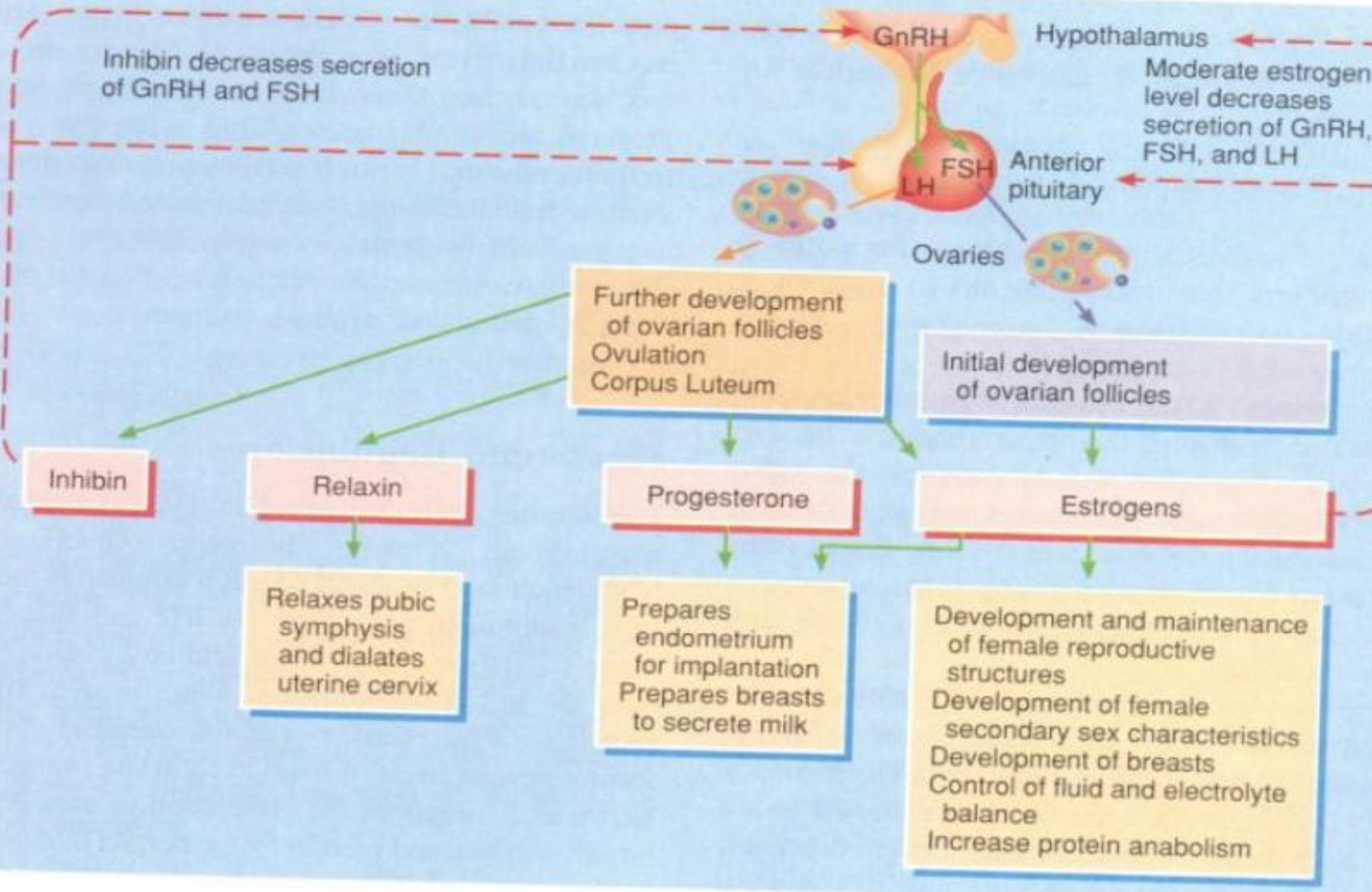
- In large quantity: Na retention (less than aldosterone)
- More often: increased Na and water excretion



Competition with aldosterone for binding with receptor so that effect of aldosterone on Na retention is blocked
with **net results increased Na excretion**

Mechanism of Action

- **The effects of progesterone, like those of other steroids are brought about by an action on DNA to initiate synthesis of RNA**
- **Progesterone receptor is bound to a heat shock protein**
- **The synthetic steroid mifepristone binds to the receptor but does not release the heat shock protein, and it blocks the binding of progesterone**
- **Mifepristone combined with prostaglandin can be used to produce elective abortions**



Secretion and physiological effects of estrogen, progesterone, relaxin, and inhibin

Thank You

Tugas

Anatomy-Physiology of Ovaries:

- Immature follicle**
- Mature follicle**
- Theca cells**
- Granulosa cells**
- Corpus Luteum**