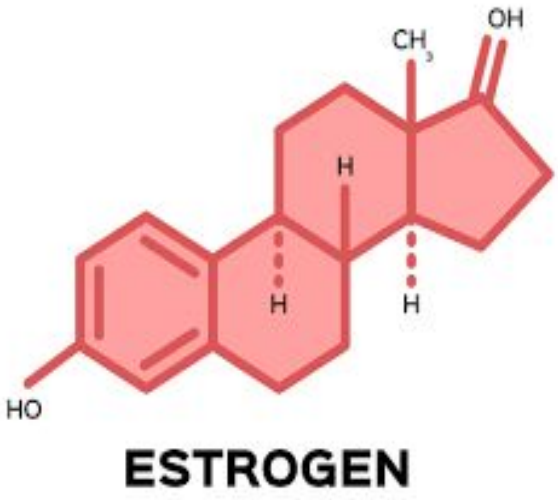
Sex (Gonadal) Hormones



Prof.Dr Sinaa Abdul Amir Kadhim

M.B.Ch.B, GP.Rad, M.Sc., Ph.D.

PROGESTOGENS

MECHANISM OF ACTION

*Progesterone **receptors** are distributed between the **nucleus** and the **cytoplasm**.

*The ligand-receptor **complex** binds to a **Progesterone Response Element** (PRE).

*Progesterone is **completely metabolized** in one passage through the liver (**not** effective **orally**).**Micronized** oral progesterone preparations provide adequate progestational effect.

Actions:

1- Prepares the uterus for implantation of the fertilized ovum.

2- Inhibit uterine contraction during pregnancy.

3- Alveolobular development of the breast secretory part.

4- -ve feed back effect on luteinizing hormone , so block ovulation.

5- Thicken the cervical secretion, so block sperm penetration.

6- Thermogenic i.e. it increases body temperature.

7- Compete aldosterone on mineralocorticoid receptor so induced sodium retention.

Preparations: Progesterone and progestins (progestogens)

Progesterone : is the

1- natural hormone.

2- not effective orally (bs of extensive 1st pass metabolism)

3- must be given by i.m injection.

4- It has a short duration of action.

Progestins :are

1- synthetic derivatives of progesterone

2- effective **orally**

3- have a **long duration** of action.

4- Some of progestins have androgenic (Progestins that are derived from 19-nortestosterone (norethindrone, norethindrone acetate, norgestrel, levonorgestrel) **, estrogenic, and even glucocorticoid-like effects.**

5- **medroxyprogesterone** acetate when injected I.M or S.C (**half-life 40 to 50 days**) and provides **3 months contraception**. The other progestins half-lives of 7 to 30 hrs, allowing once-daily dosing

	Route	Duration of Action
Progesterone and derivatives		
Progesterone	IM	1 day
Hydroxyprogesterone caproate	IM	8–14 days
Medroxyprogesterone acetate	IM, PO	Tabs: 1–3 days; injection: 4–12 weeks
Megestrol acetate	PO	1–3 days
17-Ethinyl testosterone derivatives		
Dimethisterone	PO	1–3 days
19-Nortestosterone derivatives		
Desogestrel	PO	1–3 days
Norethynodrel[2]	PO	1–3 days
Lynestrenol[3]	PO	1–3 days
Norethindrone[2]	PO	1–3 days
Norethindrone acetate[2]	PO	1–3 days
Ethynodiol diacetate[2]	PO	1–3 days
L-Norgestrel[2]	PO	1–3 days

Clinical Uses of Progestogens

- Hormone **replacement** therapy
- **Contraception**.
- When used alone in large parenteral doses, prolonged anovulation and **amenorrhea** result.
- Treatment of **dysmenorrhea (**Prostaglandin production is controlled by progesterone: **when progesterone levels drop, immediately prior to menstruation, prostaglandin levels increase**), **endometriosis** and **bleeding disorders** when estrogens are contraindicated.
- **Suppression** of postpartum **lactation** (Progesterone interferes with prolactin binding to the receptors on the alveolar cells within the breast)
- **Infertility** if due to deficiency of progesterone.
- Maintenance of **pregnancy**.

It **should not be used for patients planning a pregnancy in the near future.

Adverse Effects

1. Changes in appetite and weight gain
2. Fluid retention and swelling (edema)
3. acne
4. allergic skin rashes
5. fever, headache and depression (neurotransmitter in brain)
6. breast discomfort or enlargement
7. altered menstrual cycles and irregular bleeding.
8. Increase blood pressure in some patients.
9. The more androgenic progestins also reduce plasma HDL.

Antiprogestin

Mifepristone: is a progesterone receptor antagonist used as :

1- **Abortifacient** in the first months of pregnancy.

2- **Emergency contraceptive (**in smaller doses)

3- Breast **cancer**.

Adverse effects :

1- significant uterine bleeding

2- the possibility of an incomplete abortion

3- abdominal pain

Selective Progesterone Receptor Modulators (SPRMs)

These molecules have a **mixed progesterone receptor agonist/antagonist** profile of action in different tissues.

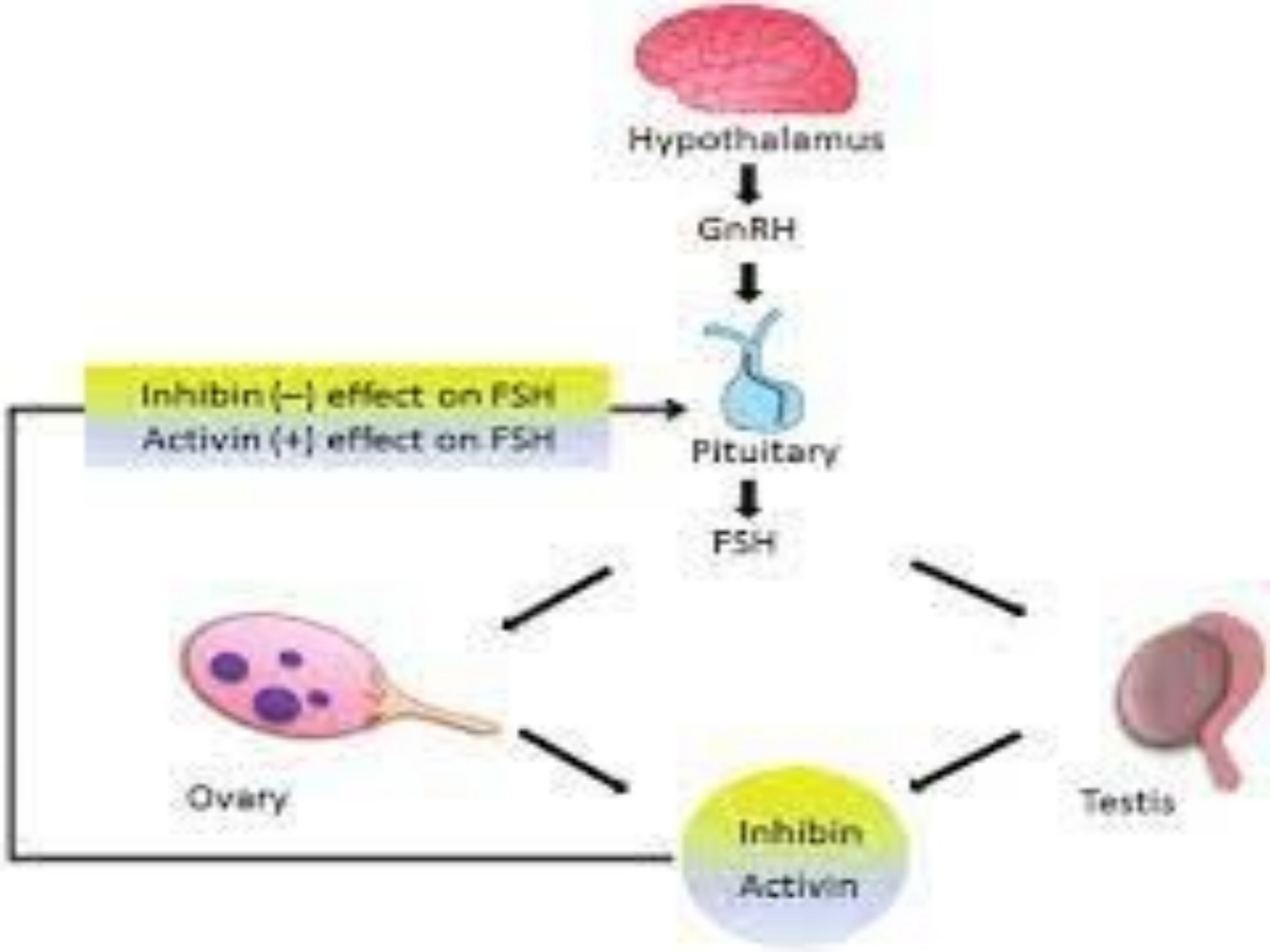
Include: Ulipristal, Asoprisnil and Proellex
Uses: uterine leiomyoma, endometriosis and uterine fibroids.

**information

OTHER OVARIAN HORMONES

The ovary also produces **Inhibin** and **Activin**. These peptides consist of several combinations of **α and β subunits**.

- The αβ dimer (**inhibin**) inhibits FSH secretion.
- the ββ dimer (**activin**) increases FSH secretion.
- **Relaxin** is another ovarian peptide. It **increases water uptake** by the myometrium and **decreases** uterine **contractility**.
- The **physiologic roles** of all these peptides are **not** fully understood.


Hypothalamus
GnRH
Inhibin (–) effect on FSH
Activin (+) effect on FSH
Pituitary
FSH
Ovary
Testis
Inhibin
Activin

Contraceptives: may be **hormonal** or **nonhormonal** (for example, condom, diaphragm and copper intrauterine device)

Types of hormonal contraceptives

1. Combination oral contraceptives (mono or triphasic)

A combination of estrogen and progestin is the most common type of oral contraceptive.

2- Transdermal patch

The contraceptive transdermal patch contains **ethinyl estradiol** and the **progestin norelgestromin**. During the 28-day cycle, one patch is applied **each week** for **3 weeks** to the **abdomen**, or **buttock**

3- Vaginal ring: it contains ethinyl estradiol and etonogestrel. The ring is inserted into the vagina and left in place **for 3 weeks**. After 3 weeks, the ring is removed

4- Progestin-only pills (the "mini-pill") contain a progestin, usually norethindrone

5- Injectable progestin: **Medroxyprogesterone** acetate is a contraceptive that is administered via **intramuscular or subcutaneous** injection every 3 months

6-Progestin implants: After **subdermal** placement in the **upper arm**, the etonogestrel implant offers contraception for up to **3 years**

7-Progestin intrauterine device: Various **levonorgestrel-releasing** intrauterine devices, effective method of contraception for **3 to 5 Years**

8-Postcoital contraception: The most common emergency contraception uses a single **high dose** of **levonorgestrel,** should be taken as soon as possible after unprotected intercourse and preferably **within 72 hours**.

Oral Contraceptives - Mechanism

- **Combination pills** act by **feedback inhibition** on the hypothalamus to **suppress GnRH** and hence plasma gonadotropin secretion. this mean Exogenously administered estrogen in contraceptives provides negative feedback which blunts release of follicle stimulating hormone (FSH) by the pituitary gland and progestin inhibits LH secretion, thus preventing ovulation.
- Progestin also thickens the cervical mucus, thus hampering the transport of sperm. Withdrawal of the progestin
- stimulates menstrual bleeding during the placebo week
- Produce an **endometrium that is unreceptive to implantation**.
- Alter **oviduct motility**.
- **Change** the composition of **cervical mucous.**
- **Block ovulation** in only ~ **25%** of women.
- **Menstruation often stops** initially with progestogens, but usually returns with prolonged use.
- But the **length** and **duration** of **bleeding** – highly **variable**.

Oral Contraceptives (OCT)

- **Uses**: - Contraception -menstrual irregularities.

- **Adverse Effects**: hypertension, diabetes, high LDL, weight gain, fluid retention, breast tenderness, breakthrough bleeding.

- **Contraindications:**

RELATIVE:- hypertension -hyperlipidemia –migraine -renal disease -diabetes (decrease insulin sensitivity) -age > 45 - smoker.

ABSOLUTE: **Thromboplebitis**, vaginal **bleeding** of **unknown** cause, **CAD, CVA**, breast **cancer**, **pregnancy**, **liver** disease or tumor.

Adrenal Sex Hormones

- **Androgens** : male hormones **secreted** by the **adrenal cortex** in **both sexes**.
- Increase protein synthesis (**anabolism**), which increase **muscle and bone mass and strength**, affect development of **male 2° characteristics**. They increase **hair growth** and **libido** in wemon. **Excessive secretion**: **masculine** effects in **women**.
- **Female sex** hormones exert **few effects**.

- The **androgen receptor** is most **closely related** to the **progesterone receptor**, and **progestins in higher dosages** can **block** the **androgen receptor**

Testosterone :

the most important androgen in humans, is synthesized by **Leydig** cells in the testes and, in smaller amounts, by thecal cells in the **ovaries** and by **adrenal gland** in both sexes

Pharmacokinetics of Testosterone:

- ineffective orally (bs first-pass metabolism).
- **administered** via a transdermal patch, topical gel or solution, buccal tablet, or implantable pellet. Esters of testosterone (example, testosterone cypionate or enanthate) are administered intramuscularly.

- The esterified formulations are more **lipid soluble** and have an increased duration of action up to several weeks

- **Inactive** metabolites are **excreted** in the **urine**.

- Testosterone and its esters have a **1:1 relative ratio of androgenic to anabolic activity**

Testosterone

Uses: Treatment of

1- low sperm count

2- impotence

3- Undescended testicles.

4- **Anabolic action** in conditions such as **osteoporosis**, **anemia** and debilitated states.

Adverse Effects: Edema, acne, hirsutism, voice deepening, polycythemia, increased LDL, depression.

Contraindications: Pregnancy, prostate cancer.

Other androgens: secreted by the testes are 5α-dihydrotestosterone (DHT), androstenedione

Finasteride and dutasteride:

they **blocks the action of an enzyme called 5-alpha-reductase**. (This enzyme changes **testosterone to another hormone dihydrotestosterone(=DHT) (DHT** that causes the **prostate to grow or hair loss in males)**.

finasteride will **increase testosterone** levels in the body, which **decreases prostate** size and **increases hair** growth on the scalp.

Testosterone aromatizes into estrogen, and because testosterone increases as a result of 5-alpha reductase inhibition, aromatization into estrogen inevitably increases as well in parallel to it.

DHT is far more androgenic than testosterone, and when there is enough of it circulating in someone prone to male pattern baldness (almost every man on earth) it results in the growth phase of the hair cycle becoming progressively shorter.

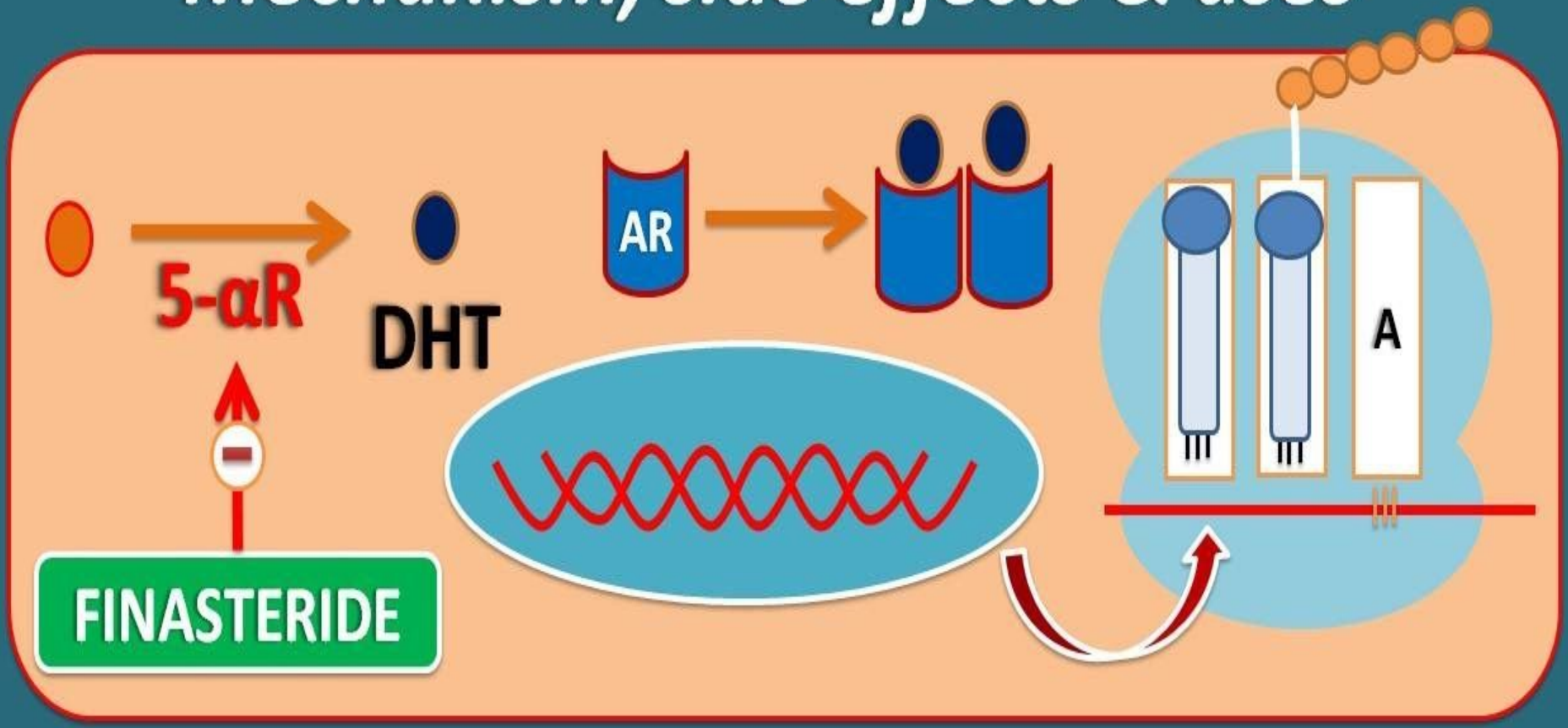
Androgen Receptor Antagonists:

Flutamide and spironolactone: used to metastatic prostate CA and BPH

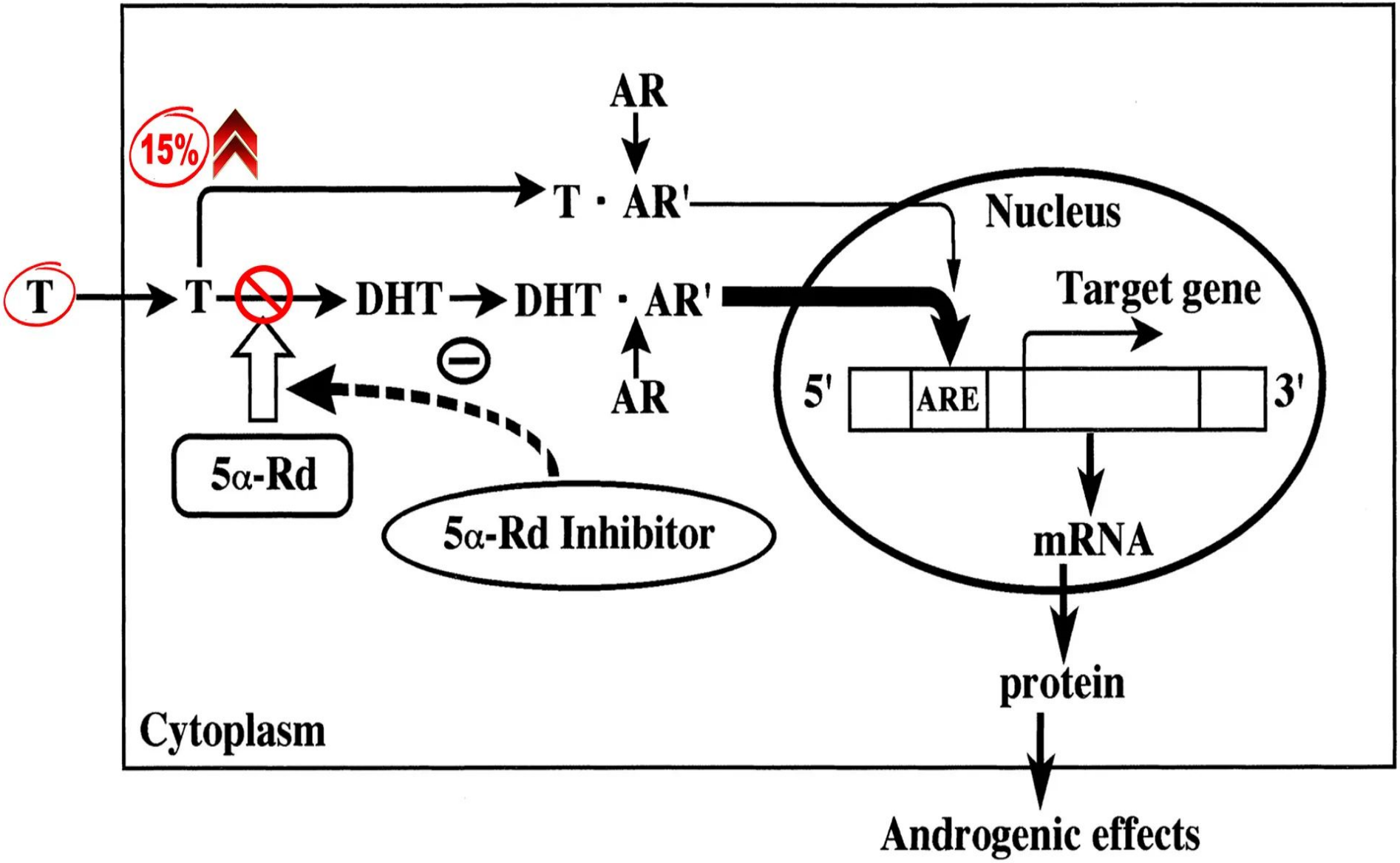
Bicalutamid, enzalutamid, nilutamide

FINASTERIDE

Mechanism, side effects & uses



T= testosteron, AR=androgen receptor



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