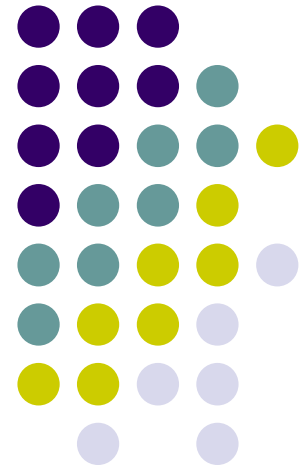


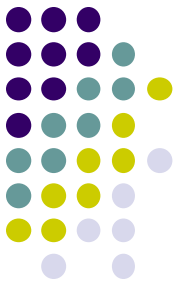
SEX HORMONES

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SEX HORMONES



- synthesised in:
 - + reproductive organs
 - + some other tissues

- two principal groups:
 - + female
 - + male

History of sex hormones



- Adolf Butenandt (1903-1995)
isolated:
 - ✚ *estrone* (1929)
 - ✚ *androsterone* (1931)
 - ✚ *progesterone* (1934)

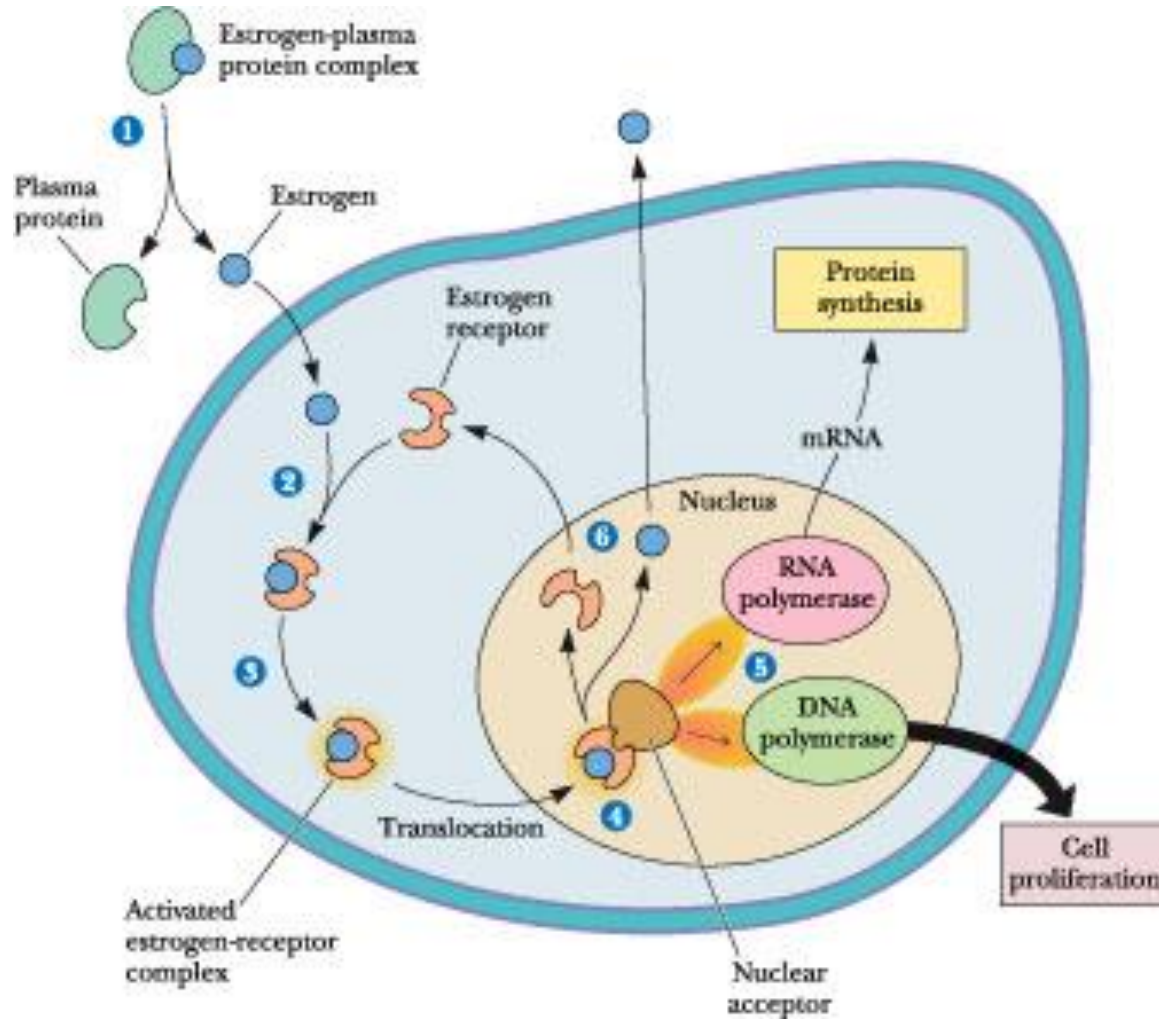
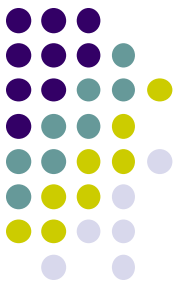
& synthesised:

 - ✚ *testosterone* (1934)
- Nobel chemistry prize in 1939



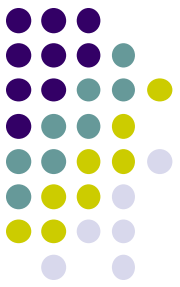
SEX HORMONES

Mechanism of action

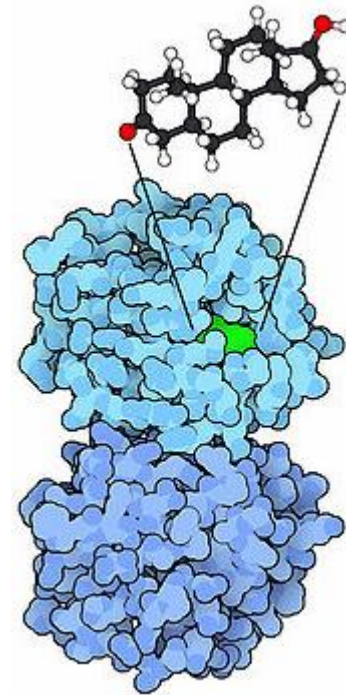


SEX HORMONES

Pharmacokinetics



- good GIT resorption
- strong plasma protein binding (globulins, albumins, transcortin)
- metabolism in liver & GIT
- preferential urine excretion mainly as glucuronylconjugates



Crystal structure of human sex hormone-binding globulin, transporting 5 α -dihydrotestosterone.

www.answers.com/topic/anabolic-steroid

ESTROGENS

Side effects



Contraceptives

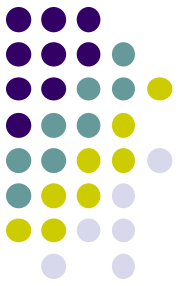
- nausea & vomiting
- ↑ risk of thrombembolic complications
- disturbance of glucose tolerance (diabetes mellitus)
- Na⁺ & water retention ⇒ edemas, ↑ body weight
- ↑ metabolism could have negative effect on liver function
- acne & ↑ pigmentation
- ↑ risk of hypertension

Substitution therapy

- incidence & intensity of side effects is lower
- ↑ risk of endometrial cancer (postmenopausal women)

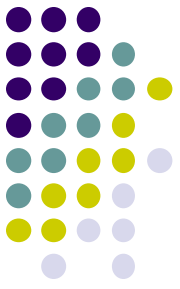
ESTROGENS

Therapeutic overview



- **ovarial hypofunction**
- **ovarial failure**
- **dysfunctional uterine bleeding**
- **primary amenorrhea**
- **breast & prostate cancer** (formerly)
- **postmenopausal symptoms**
- **suppression of lactation**
- **contraception**

CLINICAL USE OF ESTROGENS IN CLIMACTERIUM

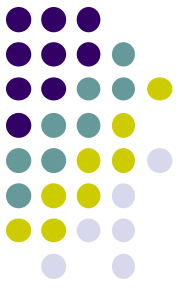


- ↓ risk of CVS diseases
- ↓ osteoporosis (up to 50% during 5 years)
- ↓ colon cancer
- elimination of menopausal sy
(e.g. sleep disorders, hotflashes)
- prevention of sex organ atrophy

Prevention of osteoporosis only is no more
the indication for estrogen use mainly for
↑ risk of breast cancer!

PROGESTERONE

Mechanism of action



- in **breast** development:
 - involved in the formation of lobular-alveolar structures
 - affects differentiation by modulation of milk protein synthesis
- in human **endometrium** PG directs:
 - glandular differentiation & glycogenesis
 - stromal proliferation & development of predecidual cells
- **PG-receptors** (PR):
 - PR - A (predominant in **uterine stroma**)
 - PR - B (predominant in **endometrial glands**)
 - A & B (equivalent in **normal breast**)

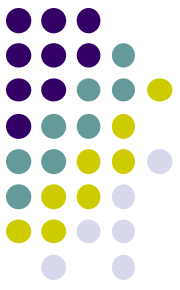
PROGESTERONE

Therapeutic overview



- mainly in *corpus luteum* insufficiency
- to induce bleeding & fast endometrium discharge
- in insufficient *progesterone* production during pregnancy
- contraception

Synthetic progestins



- ***cyproterone:***
 - synthetic progestin
 - steroidal antiandrogen & antigonadotropin
 - it is equally potent as a progestogen & antiandrogen
- ***drospirenone:***
 - synthetic agonist of the progesterone receptor
 - an antagonist of the mineralocorticoid & androgen receptors
- both often as the components of some combined oral contraceptive pills with ***ethinyl estradiol***

COMBINED oral CONTRACEPTION

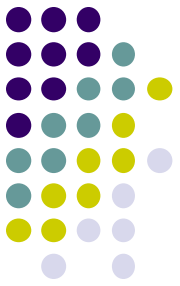
Estrogens & progesterone



- **estrogens** ↓ FSH release ⇒ ↓ ovarian follicle development
- **progesterone** ↓ secretion of LH ⇒ block of ovulation
- change in cervical mucin properties ⇒ ↓ sperm penetration
- **both hormones** influence endometrial development ⇒ invalid for egg implantation
- in consecutive 21 days ⇒ induction of menstruation

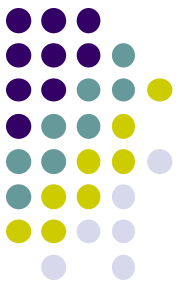
OTHER oral CONTRACEPTION

Progesterone alone



- continually during the whole period
- the effect on cervical mucin
- ↓ of egg implantation by affecting endometrium, motility & secretion of ovarial tubes
- less effective than combined contraception
- irregular bleeding (side effect)

OTHER CONTRACEPTION

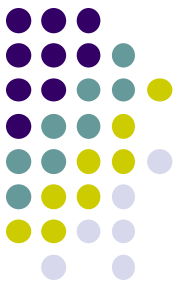


Emergency contraception (postcoital)

- high doses of hormones, the most effective ⇒
 - **estrogens & progesterone combination**
(applied immediately after coitus & repeated after 12 hours)
 - other ⇒ **high doses of estrogens** during 5 days, resp. **derivatives of progesterone only**
- the use is strictly reserved for exceptional situations (rare sexual intercourse, rape)

Ulipristal

Selective progesterone receptor modulator



Indications:

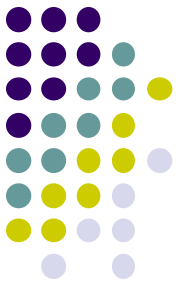
- emergency contraception - 30 mg tbl. within 120 hours (5 days) after an unprotected intercourse:
 - prevents more pregnancies than *levonorgestrel* (65 - 82%)
- pre-operative treatment of uterine fibroids (myoma)
 - effective control of excessive bleeding & reduction of the size of the fibroids

Common side effects include:

- abdominal pain & temporary menstrual irregularity or disruption
- headache & nausea (long-term administration 12 weeks)

CONTRAINDICATIONS

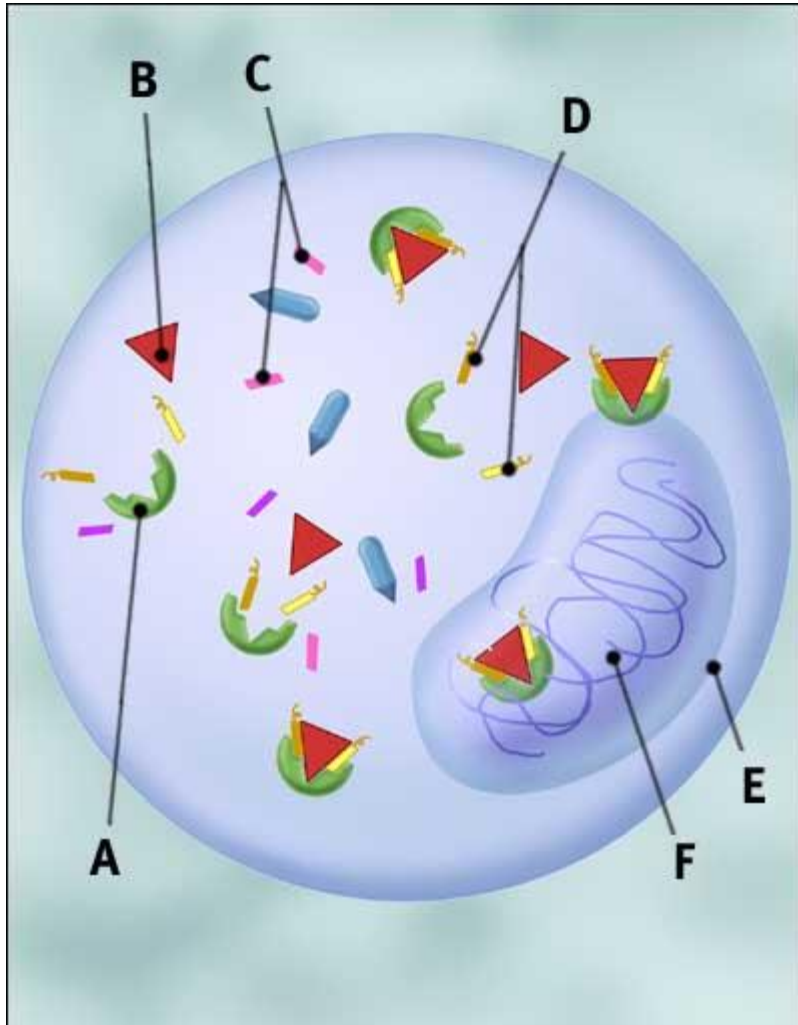
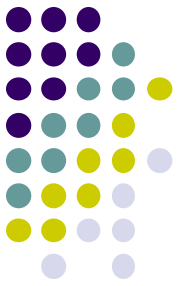
Estrogens



- **estrogen-dependent tumours**
- **thromboembolic disease**
- **hepatopathies**
- **cardiovascular & cerebrovascular diseases**

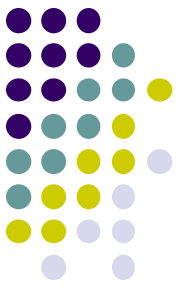
ANTIESTROGENS

Tamoxifen



- A estrogen receptor
- B tamoxifen
- C coactivator proteins
- D corepressor proteins
- E nucleus
- F DNA genetic material

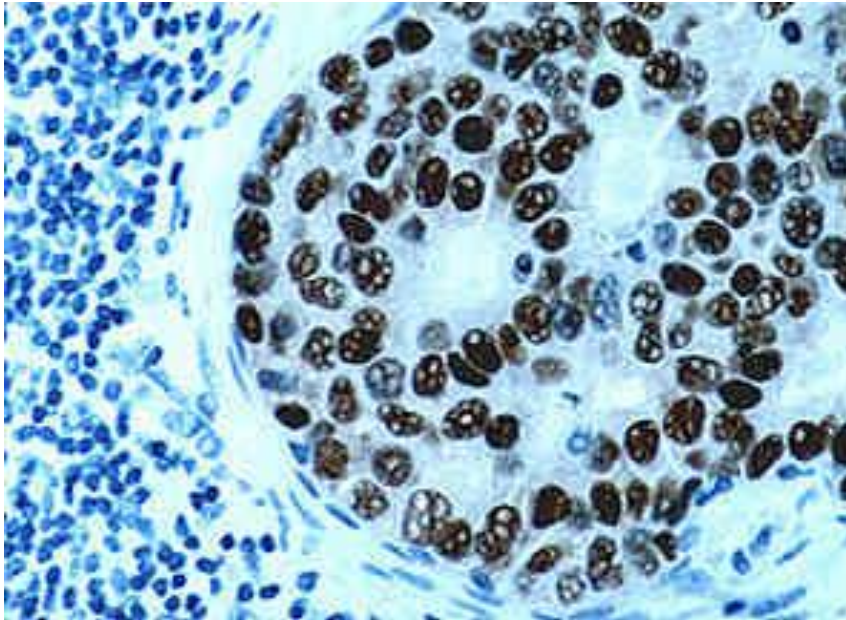
SELECTIVE ESTROGEN RECEPTOR MODULATORS



- they promote ER interactions with different proteins (transcriptional coactivators or corepressors)
- the ratio of **coactivator** to **corepressor** protein varies in different tissues
- the same ligand may be:
 - an **agonist** in some tissue (where coactivators predominate)
 - an **antagonist** in other tissues (where corepressors predominate)
- **tamoxifen as a weak estrogen (partial antagonist) is:**
 - an antagonist in breast (breast cancer treatment)
 - an ER agonist in bone (preventing osteoporosis)
 - a partial agonist in the endometrium (↑ risk of cancer)

TAMOXIFEN

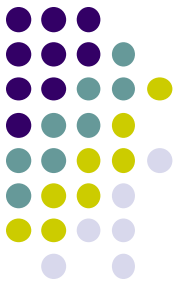
Therapeutic overview



- therapy of estrogen-dependent breast cancer
- blocks mainly the growth of estrogen stimulated tumour cells

ANDROGENS

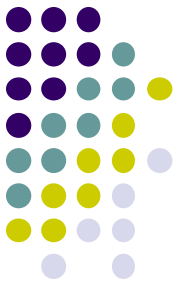
Therapeutic overview



- substitution therapy of male hypogonadism
- stimulation of growth + growth hormone (puberty)
- gynaecomastia
- anabolic effects after:
 - + severe infections
 - + surgery
 - + trauma
 - + chemotherapy & radiotherapy
- antiestrogen effect (ca mammae)
- endometriosis

ANDROGENS

Side effects



Women

- virilization (acne & hirsutism)
- irregular bleeding
- voice changes, clitoris enlargement

Preadolescent period

- faster closure of epiphyseal plate \Rightarrow growth retardation

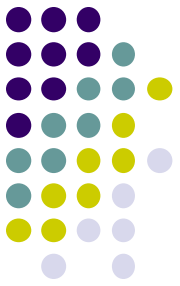
Children

- abnormal sexual development

General

- hepatotoxicity & water & Na^+ retention
- LDL increase & HDL decrease

ANTIANDROGENS



FLUTAMID

- ↓ the effect of androgens in target tissues
- therapy of hirsutism in women
- prostate cancer

