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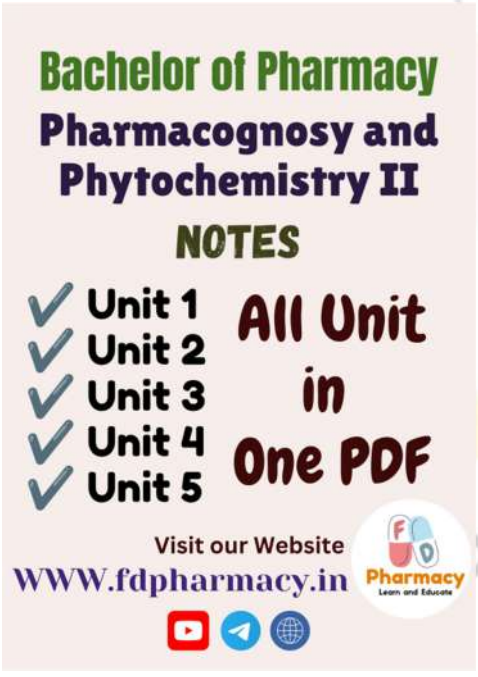
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PHARMACOLOGY - II

UNIT 5

TOPIC :

- **Pharmacology of drugs acting on endocrine system**

  a. Androgens and Anabolic steroids.

  b. Estrogens, progesterone and oral contraceptives.

  c. Drugs acting on the uterus.

Androgens and Anabolic Steroids

- Androgens are the male sex hormones responsible for the development and maintenance of male sexual characteristics.
- The main natural androgen is testosterone, secreted primarily by the Leydig cells of the testes.
- Small amounts are also produced in the adrenal cortex in both males and females.
- Anabolic steroids are synthetic derivatives of testosterone that have been chemically modified to enhance anabolic (tissue-building) effects and reduce androgenic (sex-related) effects.

Biosynthesis of Androgens

1. Cholesterol is the precursor for testosterone synthesis.
2. The biosynthetic pathway:
    - Cholesterol → Pregnenolone → Progesterone → 17-Hydroxyprogesterone → Androstenedione → Testosterone.
3. In target tissues like the prostate and seminal vesicles, testosterone is converted into dihydrotestosterone (DHT) by 5α-reductase, which is more potent.

Physiological Functions

A. Androgenic Functions

- Development of male genital organs (testes, penis, scrotum, prostate, seminal vesicles).
- Secondary sexual characteristics: facial and body hair growth, deep voice, muscle development, and increased bone mass.
- Spermatogenesis stimulation in seminiferous tubules (requires FSH + testosterone).
- Libido and sexual behavior maintenance.

B. Anabolic Functions

- Protein synthesis in muscles and bones leading to increased muscle mass.
- Nitrogen retention and positive nitrogen balance.
- Stimulation of erythropoiesis (increased red blood cell production).
- Increased calcium retention, promoting bone growth.
- Increased appetite and general sense of well-being.

Mechanism of Action

- Androgens act by binding to intracellular androgen receptors in target tissues.
- The hormone-receptor complex translocates into the nucleus, where it binds to specific DNA sequences and modulates gene transcription.
- This leads to the synthesis of specific proteins responsible for androgenic and anabolic effects.

Pharmacological Actions

System/Effect	Action of Androgens
Reproductive System	Development of male sex organs, sperm maturation
Musculoskeletal System	Muscle growth, increased strength
Skeletal System	Growth of long bones, closure of epiphyseal plates
Skin	Sebaceous gland stimulation → acne
Hair	Growth of beard and body hair, baldness (genetic tendency)
CNS	Aggression, libido enhancement
Hematopoietic System	Stimulates erythropoietin → increases RBC production

Preparations / Types of Androgens

A. Natural androgens

- Testosterone – the principal androgen, but inactive orally due to rapid hepatic metabolism.

B. Synthetic Androgens

1. Testosterone esters (for parenteral use)
    - *Testosterone propionate, enanthate, cypionate*
    - Given IM; longer duration of action.
    - Used in replacement therapy.
2. 17α-Alkyl substituted androgens (orally active)
    - *Methyltestosterone, Fluoxymesterone, Oxandrolone, Stanozolol*.
    - Resistant to hepatic degradation.
    - Used as anabolic steroids.
3. Transdermal formulations
    - Testosterone patches, gels (e.g. AndroGel) applied to skin; maintain steady plasma levels.

ANABOLIC STEROIDS

- Synthetic derivatives of testosterone designed to maximize anabolic activity (muscle growth) and minimize androgenic effects (male characteristics).

Examples:

- Nandrolone decanoate (Deca-Durabolin)
- Stanozolol
- Oxandrolone
- Methenolone
- Methandrostenolone (Dianabol)

Pharmacological Actions:

- Promote protein synthesis and muscle growth.
- Increase appetite and body weight.
- Improve nitrogen and calcium balance.
- Stimulate erythropoiesis (used in anemia).
- Enhance physical performance (abused by athletes).

Therapeutic Uses

A. Of Androgens

1. Hormone replacement therapy in:
    - Male hypogonadism (delayed puberty, impotence).
2. Palliation in breast cancer in postmenopausal women (antagonizes estrogen).
3. Osteoporosis and senile muscle wasting (rare use now).
4. Endometriosis (suppresses ovarian function).
5. Hereditary angioedema (due to stimulation of C1 esterase inhibitor).

B. Of Anabolic Steroids

1. Debilitating diseases (chronic infections, surgery, burns, trauma).
2. Osteoporosis (improves calcium retention).
3. Aplastic anemia (stimulates RBC production).
4. Growth failure in children (short-term use).
5. Post-surgical convalescence for muscle building.

Adverse Effects

A. In Males

- Testicular atrophy, decreased spermatogenesis (due to feedback inhibition of FSH and LH).
- Gynecomastia (conversion of testosterone to estrogen).
- Acne, oily skin, premature baldness.

- Increased aggression ("roid rage").

B. In Females

- Virilization: deep voice, facial hair, amenorrhea, enlargement of clitoris.
- Menstrual irregularities.
- Decreased breast size.

C. In Children

- Premature closure of epiphyseal growth plates → stunted growth.
- Early sexual development.

D. General

- Hepatic dysfunction (especially with 17α-alkylated compounds).
- Jaundice, hepatic carcinoma (with prolonged use).
- Edema and fluid retention.
- Cardiovascular risk: increased LDL, decreased HDL.
- Psychological effects: mood swings, addiction potential.

Contraindications

- Prostate or breast carcinoma in males.
- Pregnancy (causes fetal virilization).
- Liver disease.
- Nephrotic syndrome or cardiac failure (due to fluid retention).

Estrogens, Progesterone, and Oral Contraceptives

The female sex hormones — estrogens and progesterone — are secreted primarily by the ovaries and, to a lesser extent, by the placenta and adrenal cortex.

These hormones are responsible for:

- Regulation of female reproductive function
- Development of secondary sexual characteristics
- Control of menstrual cycle, pregnancy, and lactation

They are also used clinically for hormonal therapy and contraception.

Estrogens

Sources

1. Natural estrogens:
    - Estradiol (E_2): Most potent, secreted by ovaries
    - Estrone (E_1): Formed in peripheral tissues from androstenedione
    - Estriol (E_3): Major urinary metabolite during pregnancy
2. Synthetic estrogens:
    - Steroidal: Ethinylestradiol, Mestranol
    - Nonsteroidal: Diethylstilbestrol (DES), Hexestrol

Biosynthesis and Regulation

- Synthesized from cholesterol through androgens (testosterone) as intermediates.
- FSH stimulates aromatase enzyme → converts androgens to estrogens in the ovarian follicle.
- Secretion is controlled by:
    - FSH and LH from anterior pituitary
    - Negative feedback by plasma estrogen levels

Mechanism of Action

- Estrogens bind to nuclear estrogen receptors (ERα and ERβ).
- The receptor-hormone complex binds to estrogen response elements (EREs) on DNA → alters gene transcription → changes protein synthesis in target tissues.

Physiological and Pharmacological Actions

System	Effects
Reproductive system	Growth and development of uterus, vagina, and fallopian tubes; proliferation of endometrium
Secondary sexual characteristics	Development of breasts, distribution of body fat, female hair pattern
Menstrual cycle	Proliferative phase: estrogen stimulates endometrial growth
Metabolic effects	Increases HDL, decreases LDL; enhances protein anabolism
Bone	Inhibits bone resorption → prevents osteoporosis
Blood coagulation	Increases clotting factors → risk of thromboembolism
Fluid retention	Causes mild sodium and water retention

Therapeutic Uses

1. Hormone replacement therapy (HRT):
    - Menopausal symptoms (hot flushes, vaginal dryness)
    - Prevention of postmenopausal osteoporosis
2. Contraception:
    - Combined with progestins in oral contraceptives
3. Primary hypogonadism / delayed puberty
4. Dysmenorrhea and menstrual irregularities
5. Prostate cancer (palliative use)

Adverse Effects

- Nausea, vomiting
- Breast tenderness, weight gain
- Fluid retention, edema
- Thromboembolic disorders (deep vein thrombosis, pulmonary embolism)
- Endometrial carcinoma risk (if unopposed by progestin)
- Headache and hypertension

Contraindications

- Breast or uterine cancer
- Liver disease
- History of thrombosis or embolism
- Undiagnosed vaginal bleeding

PROGESTERONE

Source

- Secreted mainly by corpus luteum during the luteal phase of the menstrual cycle.
- Also produced by the placenta during pregnancy and the adrenal cortex in small amounts.

Synthetic Progestins

1. Natural: Progesterone
2. Synthetic derivatives:
    - 17α-hydroxyprogesterone derivatives: Medroxyprogesterone acetate, Megestrol acetate
    - 19-nortestosterone derivatives: Norethisterone, Levonorgestrel, Desogestrel, Ethynodiol diacetate
    - Newer progestins: Drospirenone, Dienogest

Mechanism of Action

- Progestins bind to nuclear progesterone receptors (PR-A, PR-B).
- The hormone-receptor complex regulates gene transcription → changes protein synthesis in target cells.

Physiological and Pharmacological Actions

System	Effect
Uterus	Converts proliferative endometrium (estrogen phase) into secretory type → prepares for implantation
Cervix	Thickens cervical mucus → prevents sperm penetration
Fallopian tubes	Decreases motility
Breast	Promotes lobulo-alveolar development for lactation
CNS	Sedative and thermogenic effect (↑ body temperature post-ovulation)
Metabolism	Increases basal insulin levels, promotes fat deposition

Therapeutic Uses

1. Contraception (alone or with estrogen)
2. Menstrual disorders: Amenorrhea, dysmenorrhea, endometriosis
3. Hormone replacement therapy (to oppose estrogen's endometrial effects)
4. Threatened or habitual abortion (supports pregnancy)
5. Palliative therapy of endometrial and breast carcinoma

Adverse Effects

- Weight gain, bloating
- Headache, depression
- Acne, hirsutism (with androgenic progestins)
- Menstrual irregularities
- Breast tenderness
- Decreased libido

ORAL CONTRACEPTIVES

Oral contraceptives are hormonal preparations that prevent ovulation and pregnancy by modifying the hypothalamic–pituitary–ovarian axis.

Classification

1. Combined Oral Contraceptives (COCs)

Contain estrogen + progestin.

- Monophasic: Fixed dose of estrogen and progestin for 21 days → e.g., Ethinylestradiol + Levonorgestrel
- Biphasic/Triphasic: Variable doses to mimic natural cycle → e.g., Trinordiol, Trinovum

2. Progestin-only Pills (Minipills)

- Contain low-dose progestin (e.g., Norethindrone, Desogestrel)
- Taken daily without interruption

3. Postcoital (Emergency) Contraceptives

- Levonorgestrel (1.5 mg single dose within 72 hrs)
- Ulipristal acetate (selective progesterone receptor modulator)
- High-dose estrogen (Yuzpe regimen)
- Mifepristone (antiprogestin)

4. Long-acting Progestin Preparations

- Injectable: Medroxyprogesterone acetate (Depo-Provera, every 3 months)
- Implantable: Norplant, Jadelle (Levonorgestrel implants, effective for 3–5 years)

Mechanism of Action

1. Inhibition of ovulation – suppresses LH surge and FSH release → no follicular maturation.
2. Cervical mucus thickening – prevents sperm penetration.
3. Endometrial changes – make it unsuitable for implantation.
4. Reduced tubal motility – inhibits ovum transport.

Advantages

- Highly effective (99% if used correctly)
- Regularizes menstrual cycle
- Decreases dysmenorrhea and premenstrual tension
- Reduces risk of:
  - Ovarian and endometrial cancer
  - Benign breast disease
  - Iron-deficiency anemia
  - Pelvic inflammatory disease

Adverse Effects

Type	Examples
Minor	Nausea, vomiting, breast tenderness, mild headache, weight gain
Major	Thromboembolism, hypertension, hepatic adenoma, depression, glucose intolerance
Menstrual changes	Breakthrough bleeding, amenorrhea

Contraindications

- Thromboembolic disorders
- Liver disease
- Breast or endometrial cancer
- Hypertension or heart disease
- Pregnancy
- Heavy smokers (>35 years)

Drugs Acting on the Uterus

The uterus is a muscular organ that responds to hormonal, neural, and local mediators.
Drugs acting on the uterus are primarily used to:

- Stimulate or inhibit uterine contractions
- Induce or prevent labor
- Manage postpartum hemorrhage
- Treat dysmenorrhea and uterine atony
- Manage abortion or miscarriage

These drugs mainly target uterine smooth muscle and act via oxytocin receptors, prostaglandin receptors, or adrenergic receptors.

Classification of Uterotonic Drugs (Uterine Stimulants)

Class	Example Drugs	Mechanism of Action	Clinical Use
Oxytocin & analogues	Oxytocin, Carbetocin	Activates oxytocin receptors → ↑ intracellular Ca^{2+} → uterine contraction	Induction/augmentation of labor, postpartum hemorrhage prevention
Prostaglandins	PGE1: Misoprostol PGE2: Dinoprostone PGF2α: Carboprost	Bind to uterine prostaglandin receptors → ↑ uterine tone and contraction	Induction of labor, abortion, postpartum hemorrhage, cervical ripening
Ergot alkaloids	Ergometrine, Methylergometrine	Partial agonist at α-adrenergic & serotonin receptors → sustained tonic contraction	Control postpartum hemorrhage
β2-adrenergic agonists (tocolytics)	Ritodrine, Terbutaline	Activate β2 receptors → ↑ cAMP → relax uterine smooth muscle	Delay preterm labor
Calcium channel blockers (tocolytics)	Nifedipine	Inhibit Ca^{2+} entry → relax smooth muscle	Delay preterm labor
Magnesium sulfate	$MgSO_4$	Competes with Ca^{2+} at entry channels → smooth muscle relaxation	Tocolysis, eclampsia management
Oxytocin receptor antagonists	Atosiban	Blocks oxytocin receptor → inhibits contractions	Preterm labor

Oxytocin and Analogues

Oxytocin

- Source: Synthetic or natural peptide hormone similar to posterior pituitary oxytocin.
- Mechanism of Action: Binds to oxytocin receptors → activates phospholipase C → IP_3 → ↑ intracellular Ca^{2+} → uterine contraction
- Uterine effect: Stimulates rhythmic contractions, especially in the late first stage and second stage of labor

Clinical Uses

1. Induction of labor (if labor delayed or medical reasons)
2. Augmentation of labor (when contractions are weak)
3. Prevention and control of postpartum hemorrhage
4. Medical termination of pregnancy (adjunct with prostaglandins)

Adverse Effects

- Hypotension (IV rapid infusion)
- Tachycardia or arrhythmias
- Water intoxication (with prolonged high-dose infusion)
- Uterine hyperstimulation → fetal distress

Analogues

Drug	Use	Key Feature
Carbetocin	Postpartum hemorrhage	Longer half-life than oxytocin, single dose infusion
Titrated oxytocin infusion	Labor induction	Requires close monitoring

Prostaglandins

- Derived from arachidonic acid, potent uterotonic agents.
- Act via PGE (EP) and PGF (FP) receptors in the uterus.

A. PGE1 Analogue: Misoprostol

- Oral or vaginal administration
- Mechanism: ↑ uterine contractions, softens cervix
- Uses: Medical abortion, induction of labor, postpartum hemorrhage, cervical ripening

B. PGE2: Dinoprostone

- Vaginal gel or insert
- Softens cervix (cervical ripening), stimulates uterine contractions
- Uses: Labor induction

C. PGF2α: Carboprost, Dinoprost

- Mechanism: ↑ myometrial tone → strong uterine contraction
- Uses: Postpartum hemorrhage, abortion induction
- Adverse effects: Nausea, vomiting, diarrhea, bronchospasm (caution in asthma)

Ergot Alkaloids

A. Drugs:

- Ergometrine (Ergonovine)
- Methylergometrine

B. Mechanism of Action

- Partial agonist at:
  - α-adrenergic receptors → vasoconstriction
  - 5-HT (serotonin) receptors → sustained uterine contraction
- Produces tonic uterine contraction, unlike rhythmic oxytocin contractions

C. Clinical Uses

- Prevention and control of postpartum hemorrhage
- Rarely used to induce labor (due to strong vasoconstrictive effect)

D. Adverse Effects

- Hypertension, headache, nausea, vomiting
- Vasospasm → caution in preeclampsia or cardiovascular disease
- Abdominal cramps

Tocolytic Agents (Uterine Relaxants)

Used to delay preterm labor.

Drug Class	Example	Mechanism	Key Points
β2-adrenergic agonists	Ritodrine, Terbutaline	↑ cAMP → relax myometrium	Used short-term (<48 hrs), side effects: tachycardia, palpitations, hyperglycemia
Calcium channel blockers	Nifedipine	Inhibit Ca^{2+} influx → smooth muscle relaxation	Effective and safer than β2-agonists
Magnesium sulfate	$MgSO_4$	Competes with Ca^{2+} → relax myometrium	Also neuroprotective for fetus
Oxytocin receptor antagonists	Atosiban	Blocks oxytocin receptor → inhibit contractions	Selective and safe; used in preterm labor

Other Drugs Acting on the Uterus

- Progesterone analogues (e.g., Hydroxyprogesterone caproate) → maintain uterine quiescence during high-risk pregnancy
- NSAIDs (e.g., Indomethacin) → inhibit prostaglandin synthesis → decrease uterine contractions, used in preterm labor