Pharmacognosy - 3
PHG 413

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Welcome Back Dears
You should be able to know:

- The adrenal gland
- Its function and hormone
- Sex Hormones
- Their function and hormone
VIII-The adrenal gland
The adrenal glands, as its name implies \((ad = \text{near}; \renal = \text{kidneys})\), lie atop the kidneys. Each consists of an outer portion, called the cortex, and an inner portion, called the medulla. These portions, like the anterior pituitary and the posterior pituitary, have no functional connection with one another.

### Activities are regulation of fluid volume and stress response

#### A-Adrenal Medulla

The adrenal medulla secretes norepinephrine and epinephrine under stress conditions. (normally in a ratio approximately 17:3). They bring about all those responses we associate with the "fight or flight" reaction.

The adrenal medulla is not essential for life, and no diseases of deficiency are known.

**Epinephrine**: vasoconstrictor and vasopressor responses, acting rapid onset but brief duration of action. is administered by intravenous or intramyocardial injection in cardiac arrest. Its derivation from tyrosine.

**Norepinephrine or Levarterenol**: closely related in structure & action to epinephrine. Its chief difference is its predominantly \(\alpha\)-receptor adrenergic activity. It is a strong peripheral vasoconstrictor and is especially useful in restoration of blood pressure in acute hypotensive situations. Prescription Product. Levophed®.
VIII-The adrenal gland

B-Adrenal Cortex

Although the adrenal medulla can be removed with no ill effects, the adrenal cortex is absolutely necessary to life. The Adrenal cortex secrets corticosteroids. The two classes corticosteroids are the glucocorticoids and the mineralocorticoids. The cortex also secretes a small amount of male sex hormone and an even smaller amount of female sex hormone. All of these hormones are steroids.
VIII-The adrenal gland

B-Adrenal Cortex

Regulation of Corticosteroids

• Under the effects of various stressors (physical, emotional, chemical, physiological) the hypothalamus secretes CRH ("corticotropin-releasing hormone") which acts on a portion of the pituitary gland to secrete ACTH
• The pituitary secretes ACTH ("adrenocorticotropin hormone"), which in turn
  • inhibits more CRH release by the hypothalamus (turns off the "turn-on" signal)
  • inhibits further release of ACTH from the pituitary gland, AND, most importantly...
• ACTH stimulates the release of glucocorticoids (primarily cortisol) from the adrenal gland which in turn:
  • inhibits more CRH release by the hypothalamus (as above)
  • inhibits further release of ACTH from the (par distalis region of the) pituitary gland (thus decreasing further release of cortisol)
  • exert essential physiological effects on all tissues (as described elsewhere)
VIII-The adrenal gland

B-Adrenal Cortex

Types Of Corticosteroids

a. Natural Corticosteroids
   Glucocorticoids
   –cortisol, corticosterone
   Mineralocorticoids
   –aldosterone, deoxycorticosterone
b. Synthetic corticosteroids
   Prednisolone, Betamethasone, Dexamethasone

a. Natural Corticosteroid

1-Glucocorticoids: Of the various glucocorticoids, the hormone responsible for the greatest amount of activity is Cortisol. Cortisol promotes the hydrolysis of muscle protein to amino acids that enter the blood. This leads to an increased level of glucose when the liver converts these amino acids to glucose. In opposition to insulin, therefore, cortisol raises the blood glucose level.
VIII-The adrenal gland

B-Adrenal Cortex

Types Of Corticosteroids

a. Natural Corticosteroid

1-Glucocorticoids:

*Cortisol and cortisone counteract the inflammatory response, which leads to the pain and the swelling of joints.

*The secretion of cortisol or cortisone by the adrenal cortex is under the control of the anterior pituitary hormone ACTH.

*The hypothalamus produces a releasing hormone (CRH) that stimulates the anterior pituitary to release ACTH. ACTH in turn stimulates the adrenal cortex to secrete cortisol and cortisone, which regulate their own synthesis by negative feedback of both CRH and ACTH synthesis.
Types Of Corticosteroids

a. Natural Corticosteroid
   1-Glucocorticoids:

Effect of glucocorticoids

* The glucocorticoids get their name from their effect in raising the blood sugar (glucose) level through: Stimulating gluconeogenesis in liver lead to conversion of fat and protein into intermediate metabolites that are ultimately converted into glucose.
* Decrease peripheral utilization of glucose (counteract insulin).
* Enhance lipolysis of triglycerides.
* Skeletal muscle breakdown
* Increase resorption of Ca+2 and matrix of bone.
* Anti-inflammatory
* Anti-allergic effects
* Immunosuppressive Effects (decrease the WBC’s).
* Retardation of cell division and cell growth.
* Increase hemoglobin and Red blood cells.
* Regulation of electrolytes level (Na+ & H₂O retention – Increase urinary excretion of potassium.
* Circadian rhythm.
VIII-The adrenal gland

**B-Adrenal Cortex**

**Types Of Corticosteroids**

**a. Natural Corticosteroid**

2-Mineralocorticoids

The secretion of mineralocorticoids, aldosterone and desoxycorticosterone, are not under the control of the anterior pituitary. Aldosterone is not available for therapeutic use. Aldosterone regulates the level of sodium and potassium in blood, its primary target organ being the kidney, where it promotes renal absorption of sodium and renal excretion of potassium.

**Effect of mineralocorticoids**

Aldosterone plays an important role in regulation of extracellular fluid (ECF) and blood volume and maintain K+balance. On ↓ of ECF and blood volume (e.g. hemorrhage, diarrhea) → renin release from kidney → ↑angiotensinII level → stimulation of adrenal cortex → aldosterone release → acts on kidney, sweet and salivary glands → K+excretion, Na+and H2O retention+ acts on blood vessels → vasoconstriction → ↑Blood pressure. Also, hyperkalemia stimulate its secretion, while congestive heart failure inhibit aldosterone secretion.
The potential therapeutic utility of the glucocorticoids has promoted intensive efforts to discover modifications of the naturally occurring hormones that will be more potent and more specific in their activity. The best success has been achieved with desired increases in potency. **Prednisone** (Deltasone®, Meticorten®) and **prednisolone** (Delta-Cortef®, Sterane®) represent early achievements in these efforts.

Elimination of any mineralocorticoid activity has been a major objective; a degree of success has been attained with such compounds as: **betamethasone** (Celestrone®) **dexamethasone** (Decadron®, Dexone®, Hexadrol®) **methylprednisolone** (Medrol®) **paramethasone** (Haldrone®) **triamcinolone** (Aristocort®, Kenacort
Short-term stress response

1. Glycogen broken down to glucose; increased blood glucose
2. Increased blood pressure
3. Increased breathing rate
4. Increased metabolic rate
5. Change in blood-flow patterns, leading to increased alertness and decreased digestive and kidney activity

Long-term stress response

**Mineralocorticoids**
1. Retention of sodium ions and water by kidneys
2. Increased blood volume and blood pressure

**Glucocorticoids**
1. Proteins and fats broken down and converted to glucose, leading to increased blood glucose
2. Immune system may be suppressed
VIII-The adrenal gland

**Disease Status**

1. **Addison’s disease** (due to Adrenal insufficiency or Hypocortisolism): rare 1/100000
   - **Causes:** Low level of ACTH - Atrophy of adrenal gland – Tuberculosis $\rightarrow$ $\downarrow$ cortisol and $\downarrow$ aldosterone (hypoaldosteronism) levels.
   - **Symptoms:** Weakness, fatigue, apathy, depression and irritability. Anemia and low blood pressure. Loss of sodium and dehydration. Hyper pigmentation.

2. **Hyperaldosteronism** (syndrome caused by elevated aldosterone) generally results from adrenal cancers.
   - **Symptoms:** Excessive Na+ and H$_2$O retention $\rightarrow$ Hypertension and edema. Accelerated excretion of K+ $\rightarrow$ hypokalemia $\rightarrow$ muscle weakness and eventually paralysis.

3. **Cushing’s disease** (due to Hypercortisolism): Rare 2-5/Million.
   - **Causes:** Tumor of Adrenal Cortex or Pituitary gland or Iatrogenic cause (physician caused)

4. **Conn’s syndrome**:
   - **Causes:** Inability of adrenal cortex to carry out the 17a-hydroxylation of pregnenolone. That leads to low level of Cortisol and high level of Aldosterone.
   - **Symptoms:** Hypertension. Alkalosis. Polyuria. Edema.
VIII-The adrenal gland

Clinical use of Glucocorticoids


Side effects of Glucocorticoids

Due to Prolonged use:

Withdrawal Symptoms:
If corticosteroids are taken for a long time, it should be gradually reduced in 5-7 days to allow the adrenals time to recover and begin normal cortisol production, otherwise symptoms of severe hypoadrenalism may happen e.g. extreme fatigue, weakness, stomach upset, dizziness, etc
The adrenal cortex produces a small amount of both male and female sex hormones. In males, the cortex is a source of female sex hormones, and in females, it is a source of male hormones.

A tumor in the adrenal cortex can cause the production of a large amount of sex hormones, which can lead to feminization in males and masculinization in females.
IX-Sex Hormones

Cholesterol → Pregnenolone → Progestogens → Androgens

Pathway for steroid hormone synthesis in TESTIS and OVARY

Oestrogens in OVARY
Testosterone in TESTIS

Oestrogen: breasts grow, pubic hair grows, wide hips develop

Testosterone: body hair grows, voice breaks, muscle growth increases

Progesterone

Final products
IX-Sex Hormones

Female sex hormones

(Estrogens and Progestagens)

1-Estrogens are 10-demethylated C18 steroids with an aromatic A ring (produced from androgens by enzymatic actions).

Estradiol is the predominant form in non-pregnant females, estrone is produced during menopause, and estriol is the primary estrogen of pregnancy.

2-Progestagens: have C21 skeleton and function in maintaining pregnancy (support gestation), although they are also present at other phases of estrous and menstrual cycles. Exogenous or synthetic hormones are called progestins.

Regulation of female sex hormones

- FSH stimulate the production of Estrogens.
- LH stimulate the production of Progestagens.
IX-Sex Hormones

Female sex hormones

1. Estrogens

- Biosynthesized in ovary, placenta, adrenal cortex & testes.
- Estradiol (most potent estrogen) : estrone : estriol = 10 : 5 : 1
- Oral estradiol has short duration of action due to first pass liver metabolism into the less active estrone and estriol. So, estrogen analogs (with a different chemical structure) must be used for effective oral estrogen therapy.

Function of Estrogens

a. Development of the female sexual organs.
c. Control of the menstrual cycle.
   - Required for optimal progesterone effects (e.g. in uterus).
   - Accelerate maturation of ovarian follicle.
   - Promote the proliferation of the endometrium.
   - Thickens the mucosa of vagina → ↑ glycogen discharge → ↑ lactic acid production by Döderlein’s bacillus → acidic pH → ↓ vaginal infection.
   - Make cervical mucus conducive to sperm penetration and survival, especially around the time of ovulation.
IX-Sex Hormones

Female sex hormones

1. Estrogens
d. Extra gonadal effect of estrogens.
- Slow longitudinal bone growth.
- Accelerate epiphyseal closure (in men and women) and ♦ osteoblast activity. Therefore, estrogen deficiencies in menopause → loss of bone mass (osteoporosis).
- Induce ♦ LDL and ♦ HDL (arteriosclerosis is less common in premenopausal women than in men).
- Influences a number of central nervous functions, e.g. sexual response, social behavior, and mood.

Use of Estrogens
1. Birth control.
2. Failure of ovarian development.
3. Menstrual disturbances.
5. Postmenopausal osteoporosis.
6. Prostate cancer.

Side Effects
1. Nausea, vomiting and diarrhea.
2. Sodium and water retention.
3. Inhibition of ovulation in large doses.
IX-Sex Hormones

Female sex hormones

Steroidal Estrogenic Drugs

1. Estrogens
   - Most active natural estrogen.
   - Very short duration of action due to first pass metabolism.
   - As replacement therapy at the beginning of menopause or after oophorectomy in combination with a progestin.
   - Treatment of infertility in women due to sperm-unfriendly cervical mucus or inappropriate uterine lining (in combination with Clomid).
   - Also used for local effect on uterus.

2. Ethinylestradiol
   It is 15-20 more potent than estradiol alone
   - Most frequently used as an estrogen component of combined oral contraceptives.
   - Also used for the treatment of menopausal and post menopausal symptoms, especially the vasomotor effects.
Nonsteroidal Synthetic Estrogens

**Diethylstilbesterol** (Stilboestrol®, 5mg/day): The *trans* form is the active one.

**Uses:**
1. Treatment of advanced prostate cancer, where the cancer has spread beyond the prostate gland – for example, to the bones.
2. Treatment of advanced breast cancer in postmenopausal women.

**Advantages:** As active as Estradiol. Longer duration of action. Orally active. Cheap.

**Disadvantages:** Increase the risk of uterine cancer.

Nonsteroidal Natural Estrogens (Phytoestrogens)

Estrogenic compounds with weak activity present in herbs, food and drinks. 
- Isoflavones and comesterols derivatives, present in family Leguminosae (e.g. Soya, Fenugreek), are examples of phytoestrogens.
- Phytoestrogens exert their effects primarily through binding to estrogen receptors.
- The similarities, of estrogens and phytoestrogens allow them to mildly mimic and sometimes act as antagonists of estrogen.
- Evidences showed that phytoestrogens (dietary estrogens) may protect against diverse health disorders such as prostate, and cancers, cardiovascular disease, and osteoporosis
IX-Sex Hormones

Female sex hormones

**Estrogens Antagonists**

They act by

1. Competitive antagonism with estrogen at the estrogenic receptors e.g. Triphenylethylene antagonists (Tamoxifen):

**Uses**: Treatment of both early and advanced estrogen receptor positive (ER+) breast cancer in pre- and post-menopausal women. Additionally, it is the most common hormone treatment for male breast cancer

2. Enzymatic inhibition of biosynthesis of estrogen from androgens e.g. aromatase inhibitors:

   - They are two types:
     - Steroidal Irreversible inhibitors by forming permanent complex with the aromatase enzyme (ex. Exemestane).
     - Non-steroidal reversible inhibitors which inhibit the enzyme by reversible competition. (ex. Anastrozole)

   **Uses**: Treatment of both breast cancer with or without tamoxi
Progestagens

Progesterone, the most potent pro-gestational (pregnancy-sustaining) hormone, is produced by corpus luteum (during the 2nd ½ of menstrual cycle), placenta, and adrenal cortex of male and female.

Like estradiol, oral doses of progesterone are almost ineffective due to rapid metabolism by liver.

**Physiological Functions of progesterone**

1. Prepare uterus for implantation and maturation of fertilized ovum and to sustain pregnancy (main function) with associated changes:
   - Stimulates growth of myometrium.
   - Stimulate formation of secretory endometrium (at day 22 of the cycle).
   - Reduce myometrial activity (important in pregnancy), narrows cervix, and make cervical mucous plug to be sperm impregnable.

2. Its administration during the follicular phase inhibits ovulation. This with its effects on the cervix, progesterone therefore have contraceptive effect.

3. It exerts thermogenic action (raises basal body temperature).


5. Milk secretion starts when its level decrease with birth.

6. It slightly inhibits aldosterone effect (inducing increased NaCl excretion)

7. Its decrease is responsible for the mood changes and depression observed before menstruation (premenstrual syndrome) and after pregnancy (postpartum depression)
2. Progestagens

Drug formula of Progestagens

Progestins

Lynestrenol (Orgametril®)
- It is semisynthetic progestin with pure progestrogenic activity
- After oral administration lynestrenol is quickly resorbed and converted into pharmacologically active Norethisteron.

Uses of Lynestrenol and Norethisteron

Progestin Antagonists

Mifepristone
It Compete with the progesterone receptors.

**IX-Sex Hormones**

**Female sex hormones**

**Female Oral Contraceptives**

**1. Sequential Preparations:**
- Estrogens for 16 days then Estrogen and Progesterone for 5-6 days.
- 98-99% successful.

**2. Combination Preparation:**
- Estrogens and Progesterone from beginning to end.
- 99-100% successful.

**Mechanism:** The above two types inhibit both FSH and LH to prevent ovulation.

**3. Minipills:**
- Small doses of Progesterone from beginning to end.
- 97-98% successful.

**Mechanism:** Alter the structure of the Endometrium and Increase consistency of the cervical mucus.

**Side Effects of oral contraceptive (Due to Estrogens)**
- Increase risk of breast, vaginal and uterine cancers.
- Increase risk of thromboembolic and vascular problems.
- Nausea, vomiting, headache, menstrual disturbances and weight gain.
Male sex hormones

Male Reproductive Hormones: Androgens, androsterone & testosterone

Testosterone is the main sex hormone in the male and is secreted in the testes.

After receiving the command, the pituitary gland secretes two hormones, LH and FSH. The target areas of these hormones are the female ovaries and the male testes.

The testes and ovaries then begin to produce the sex cells proper to males and females and to secrete the sex hormones. The LH and FSH hormones in men and women have the same molecular structure, yet each is responsible for different processes in the male and female bodies.

Regulation of Male Sex Hormones

Regulation of Male Sex Hormones Bloodstream Hypothalamus GnRH FSH LH Inhibin Testes Stimulation Inhibition Androgens prevent over-secretion of GnRH Androgens prevent over-secretion of LH Inhibin prevents over-secretion of FSH Androgens stimulate the development of male secondary sex characteristics and maturation of sperm cells Testosterone and other androgens FSH stimulates meiosis in primary spermatocytes to form immature sperm cells; FSH stimulates secretion of inhibin by supporting cells LH stimulates interstitial cells to secrete androgens (primarily testosterone) Pituitary gland Release into bloodstream
Male sex hormones
(Androgens)

Uses of Testosterone
- Hormone replacement therapy in cases of hypogonadism (little or no natural endogenous testosterone production).
- Anabolic and muscle builder.
- Prevention or reduction of type II diabetes, cardiovascular disease, obesity, depression and anxiety.
- Women may also use testosterone therapies to treat or prevent loss of bone density, muscle mass and to treat certain kinds of depression and low libido state.
- Appetite stimulation and bone marrow stimulation.
- Not used by oral administration (why?)

Side Effect
- Sodium and water retention leads to edema.
- Masculinization of women.
- Hepatic dysfunction.
- Erythro-cytemia (abnormal increase of erythrocytes in the blood) and increase in blood thickness.
IX-Sex Hormones

Male sex hormones

Androgenic Drugs (testosterone analogs)

17 a-methyltestosterone (methyltestosterone)
Semisynthetic. Orally active. Prolonged action. Androgenic and anabolic effects

Oxandrolone and Norethandrolone
- Orally active.
- Anabolic effects.
- Methyl group at C-10 in Norethandrolone is removed to eliminate androgenic effect.

Androgen Antagonists

They act either by competition with androgens at the androgenic receptors or by inhibition of androgens biosynthesis.

1. Androgen Receptor Antagonists:
Cyproterone acetate: Has antiandrogenic and progestogenic activity. Used for treatment of acne, hirsutism, prostate hypertrophy, prostate cancer and precocious puberty.
**IX-Sex Hormones**

**Male sex hormones**

**Androgenic Drugs (testosterone analogs)**

**Androgen Antagonists**

2. Androgen Biosynthesis inhibitor
   - 5α-Reductase inhibitors
   - They prevent conversion of testosterone into dihydrotestosterone.
   - Used for treatment of Benign Prostatic Hyperplasia, androgenic Alopecia, and prostate cancer
   - Examples: (aza-androst-1-ene derivatives)
     - Finasteride (Proscar®, Propecia®)
     - Dutasteride (Avodart®)

**Male Contraceptives**

**Gossypol:**
- It is a phenolic compound present in cotton seed oil.
- Decrease number of sperms and impairs their motility.
- Its effect is reversible.

**Side Effects:** Hypokalemia, weakness, diarrhea, and edema.

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It has been abandoned now for the contraceptive use because it was found to cause permanent infertility in 10-20% of users.
Thanks