endocrine system

Pharmacology

Sheet Slide

number **3**

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Correction

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The adrenal glands

They are present at the superior border of each kidney; they are different in shape but identical in composition and function. Each one is composed of:

1-Cortex has three layers:
→ Zona glomerulusa: it is the outermost layer and secretes mineralocorticoids, mainly aldosterone.
→ Zona fasciculate: it is the intermediate layer and secretes glucocorticoids, mainly cortisol.
→ Zona reticularis: it is the innermost layer and secretes sex hormones.

2-Medulla: secretes epinephrine (80%) and norepinephrine (20%).

In this lecture, we are going to discuss the mineralocorticoids and the glucocorticoids only. The sex hormones will be discussed in the urogenital system next semester.

Mineralocorticoids (Aldosterone)

They are hormones that affect the metabolism of minerals. Aldosterone is the main hormone of this family and controls body fluid volume and the metabolism of K+ and Na+.

➢ Synthesis of Aldosterone:

Cholesterol ---*DE---> Pregnenolone ---*DeH**---> Progesterone ---*Hyd.21**---> Deoxycorticosterone ---*Hyd.11**---> Corticosterone ---*Hyd.18**---> Aldosterone.**

**DE*: Debranching enzyme, side chain cleavage enzyme, or dismolase.

**DeH*: 3B-Hydroxysteroid Dehydrogenase enzymes.

**Hyd*: Hydroxylase.

NOTE Hormones of the adrenal cortex are synthesized from cholesterol by multiple steps. This multiplicity in steps subjects the pathway of synthesis to many minor defects like enzymes deficiencies caused by genetic influences.

➢ Control of synthesis and release of aldosterone:

- ↑ Angiotensin II and angiotensin III.

- ↑ K^+ (the most sensitive stimulator of aldosterone).

- ↑ **ACTH** from the pituitary gland and consequently ↑ **CRH.** (Since CRF stimulates ACTH release).

- ↓ ECF or blood volume.

- ↑ Metabolic acidosis or pH.

➢ Renin-angiotensin-aldosterone axis:

Renin is released from the juxtaglomerular apparatus in kidneys, it converts angiotensinogen to angiotensin I, which in turn is converted to angiotensin II by an enzyme called angiotensin converting enzyme (ACE) in the lungs. This is called RAAS (renin-angiotensin-aldosterone-system) and its stimulated by many factors including:

- **Volume depletion** (hemorrhage, low Na+ intake, dehydration, overuse of diuretics…).
- **Upright posture**
- **K**+. High potassium will stimulate renin release.
- **ACTH** and consequently **CRH**
- **Vasodilators**
- **Beta adrenoreceptor agonists**

Also, this system is inhibited by:

- **Blood volume expansion**.
- **Renin release inhibitors**, aka renin antagonists, such as: Aliskiren, Remikerin, Enalkiren and beta-1 blockers.
- **ACE inhibitors**, e.g. Captopril, Enalapril and Benazapril.
- **ARB's** (angiotensin II receptor blockers), e.g. Candesartan, Losartan, Irbesartan and Telmesartan.
- **Aldosterone antagonists**, e.g. Spironolactone (which as an important diuretic) and Eplerenone.

➢ Effects of aldosterone:

Aldosterone effect is receptor mediated and these receptors are present on the *distal* convoluted tubules in the kidneys. Aldosterone increases the reabsorption of Na+, which results in hypertension. It also increases the excretion of K+ and H+, which leads to hypokalemia and metabolic alkalosis.
The increase in Na+ reabsorption along with the increased K+ and H+ excretion will consequently increase the extracellular volume and blood pressure.

NOTE Increased Na+ reabsorption → increased water reabsorption → increased plasma volume → increased BP.

NOTE Aldosterone itself has no clinical application, nor therapeutic and pharmacological indications. Usually, diseases of the adrenal cortex don't cause deficiency of the Aldosterone alone, they cause deficiency in all the cortical hormones (aldosterone, cortisol ..). so the treatment is done by replacement therapy of all the cortical hormones, not only aldosterone. Though, in certain conditions, we need to suppress only the Aldosterone activity.

Glucocorticoids (Cortisol)

Also secreted from the adrenal cortex, under the influence of the ACTH from the anterior pituitary and CRH from the hypothalamus. Under physiological conditions, High concentrations of cortisol will suppress the secretion of ACTH and CRH by feedback inhibition, whereas low levels of cortisol will cause more secretion of ACTH and CRH.

When we use high doses of cortisol for a long period of time there will be suppression of ACTH and CRH causing rearrangement of the physiological axis (CRH→ACTH→Cortisol). There will be a chronic suppression that pushes the homeostatic line into a new one. When we stop administering the drug there will be a lag period during which the original axis is being reactivated and the homeostatic line is recovered, this lag period is called **withdrawal syndrome** and it is due to desensitization of the receptors. This mechanism is more evident with drugs of abuse like morphine and the smokers.

Cortisol secretion follows a circadian rhythm, usually high in the morning and low in the evening. The treatment should mimic this rhythm when we take cortisol in small physiologic doses as replacement therapy.

We also give cortisol in large pharmacological and therapeutic doses in the treatment of severe inflammatory diseases for example.

➢ Synthesis of Cortisol:

Cholesterol---*DE*---**>Pregnenolone**---*DeH*---**>Progesterone**---*Hyd.17*---**>Hydroxyprogesterone**---*Hyd.21*---**>Deoxycorticosterone**---*Hyd.11*---**>Cortisol.**

➢ Steroid synthesis inhibitors:

1-O, P'-DDD (**Mitotane**):
Causes selective atrophy of zona fasciculate and zona reticularis.
Useful in **adrenal carcinoma**; because it usually involves more than one layer, when radiotherapy or surgery are not feasible and in **certain cases of breast cancer**.

2-**Aminoglutethimide**:
Selective desmolase inhibitor and non-selective aromatase inhibitor.
Same uses as mitotane

3-**Trilostane**:
3B-hydroxysteroid dehydrogenase competitive inhibitor.
Effective in **Cushing's syndrome** (which is caused by high levels of corticosterone) and **breast cancer**.

4-**Ketoconazole**: (Antifungal agent)
Different hydroxlases inhibitor.
Inhibits steroidogenesis in adrenals and testes.
Effective in **Cushing's syndrome** and **carcinoma of prostate.**

5-**Amphenone B**:
Different hydroxylases inhibitor.
BUT **very toxic** so causes: anti-thyroid effect, CNS depression, GIT upset and skin disorders.

6-**Metyrapone** (**Metopirone**):
11B-hydroxylase inhibitor.
Diagnostic tool (**Metyrapone test**) in conditions of hypo- or hyper-secretion of the adrenal glands.
Effective in **Cushing's syndrome.**

➢ Action of Glucocorticoids:

→On proteins: increase catabolism and decrease anabolism so it is a **catabolic hormone** causing osteoporosis, myopathy, delayed wound healing and delayed peptic ulcer healing.

→On carbohydrates: they cause a condition which looks like diabetes, so it is considered as a **diabetogenic hormone**; due to gulconeogenesis and decreased peripheral utilization of glucose. As you know, many hormones are diabetogenic like Thyroxin and GH.

→On lipids: enhance **lipolysis** which results in **body fat redistribution** that gives the appearance of Cushing's syndrome patient.

→On electrolytes:
Aldosterone-like effect but less potent (Na and H2O retention and K excretion).
Decreases calcium absorption from intestine, and this is anti-vitamin D effect.
Increase calcium and uric acid excretion by kidney.

→Anti-inflammatory effect (the most important effect):
They affect phospholipids conversion to Arachidonic acid by the enzyme phospholipase A2; they can suppress this enzyme causing disturbances in the generation of COX and LOX pathways which are important in the integrity of the inflammatory processes.
As you know, inflammatory reactions are protective mechanisms, but in cases of exaggerated and prolonged inflammatory reactions, many disturbances or many signs and symptoms which are manifested as diseases will develop. In such cases, we need to reduce the inflammation rather than affecting the real etiology of the disease. So we use glucocorticoids, and this is their main therapeutic use.

Other possible anti-inflammatory mechanisms:
- Inhibition of neutrophils and macrophages function.
- Inhibition of platelet activation factor PAF.
- Inhibition of tissue necrosis factor or receptor TNF or TNR.
- Inhibition of NO reductase.

All of these effects will contribute in the significant anti-inflammatory activity either in health or in disease.

NOTE Glucocorticoids have Aldosterone-like effect. So the major objective of synthesizing glucocorticoidal drugs is to produce good anti-inflammatory drugs with less or no aldosterone-like activity.

→Immunosuppressant effect:
Decrease initial processing of antigens.
Decrease antibody formation.
Decrease effectiveness of T-lymphocytes.
Decrease induction and proliferation of lymphocytes (the number of lymphocytes).
Decrease lymphoid tissue including leukemic lymphocytes (**Anti-leukemic effect**),
So it is effective in the treatment of certain types of leukemia when they are of lymphocytic origin such as acute lymphoblastic leukemia and chronic lymphocytic leukemia. glucocorticoids are not considered as anti-cancer drug but they are the major drug used beside anti-cancer drugs.

→Anti-allergic effect:
Suppress allergic response by **decreasing histamine release** and by **decreasing eosinophils** in the allergic response.

→CNS effect: they might have **euphoric** activity as well as **Psychotic** activity.

➢ Glucocorticoids dosages and metabolism:

Glucocorticoids are available in all dosage forms (oral, IV, local …) and can be used alone or in combinations. In osteoarthritis treatment, glucocorticoids are used in combination with non-steroidal analgesics and local anesthetics as injections to temporarily relief the pain and decrease the symptoms. Also, they are used with antifungal and antibacterial drugs.

Glucocorticoids preparations are divided into three groups according to their half-life:

A) Short-acting: have an average half-life of 10 hours and include cortisol (the natural hormone produced by the body), cortisone, corticosterone and fludrocortisone. As we said earlier, we need agents that have good anti-inflammatory effect with less or no Aldosterone-like activity, unfortunately, these short-acting agents have the same or higher aldosterone-like activity. Fludrocortisone for example is 150 times more effective than aldosterone in salt and water retention. Usually, these agents aren't used as anti-inflammatory drugs, but as replacement therapy.
B) Intermediate-acting: they have an average half-life of 20 hours (given once daily). They have higher anti-inflammatory activity and less Aldosterone-like activity than cortisol, so this group is used therapeutically (to suppress inflammation, allergic reactions and tumor activities), and includes prednisone, prednisolone, methylprednisolone, triamcinolone and beclomethasone.

C) Long-acting: they have an average half-life of 50 hours. Their anti-inflammatory activity is high (25-30 times higher than cortisol) with ***no*** Aldosterone-like effect.

Glucocorticoids are metabolized in the liver either by reduction and conjugation (90-95%) or hydroxylation reactions (5%).

➢ The clinical uses of glucocorticoids:

→**Adrenal insufficiency**: e.g. acute and chronic Addison's disease. Given in small physiological doses as replacement therapy.

Patients and even doctors are usually worried about giving steroidal drugs. But there should be no worry when giving these drugs in small doses.

→ **Inflammatory conditions:** e.g. rheumatoid arthritis, SLE, arteritis, dermatomyositis, cerebraledema, ulcerative colitis rheumatic carditis, active chronic hepatitis and proctitis.

In such cases, we give high doses of glucocorticoids, so their level must be monitored and the patient must be followed up.

→ **Allergic reactions:** e.g. hay fever, eczema, status asthamticus and bronchial asthma.

→**Immunosuppression**: organ transplantation, hemolytic anemia, leukemias, many tumors.

→**Hypercalcemia:** associated with Vit. D intoxication or sarcoidosis or hyperparathyroidism or cancer.

➢ Side effects of glucocorticoids:

→Suppression of the hypothalamic-pituitary-adrenal axis.

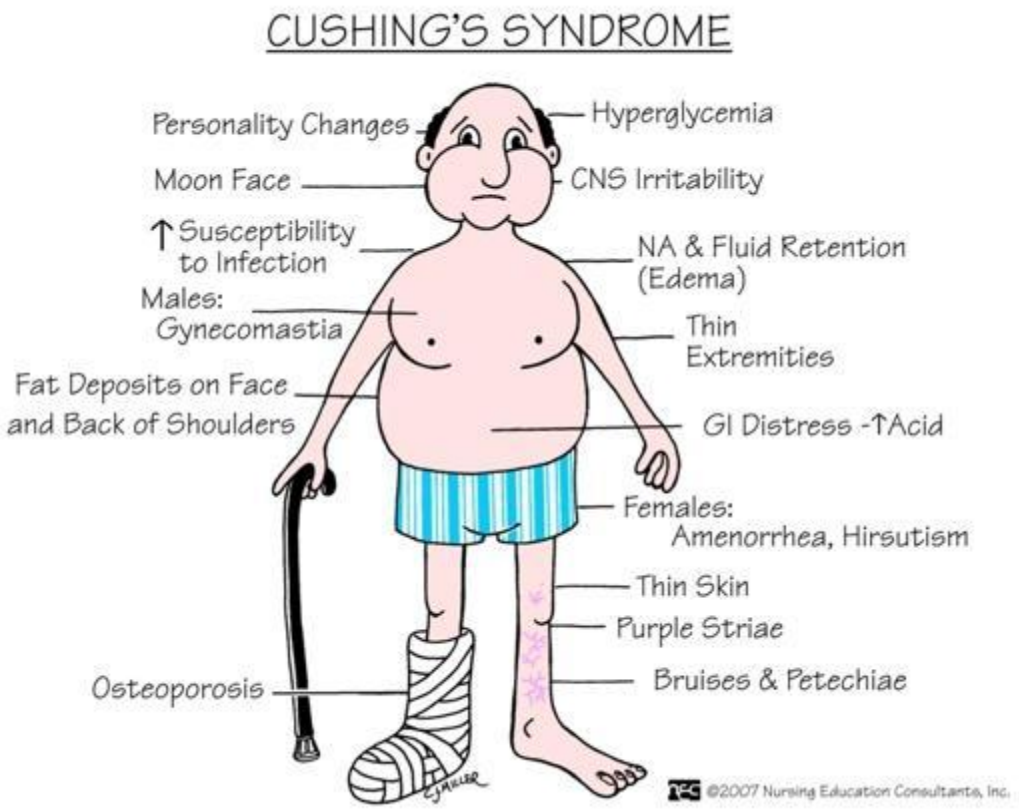
It's the most dangerous side effect and caused by the administration of high doses that cause feedback inhibition and suppression of this axis. If the administration continued for more than two weeks, the patient must be given supplementary therapy at times of stress, since the glands are suppressed.

NOTE when there is a stress, these glands give bursts (pulses) of hormones to cope with the situation. But when these glands are suppressed, their corresponding hormones will be missing, and supplementary therapies must take place. Such

therapies are achieved by giving the patient the needed hormones (the missing hormones due to the suppression).

Treatment of this suppression is done by ***slowly tapered*** reduction of the administered glucocorticoid. Reducing the doses **rapidly** will cause the symptoms of the disorder to reappear or increase in intensity. Also, withdrawal syndrome appears which includes: anorexia, nausea, Vomiting, weight loss, lethargy, headache, fever, joint and muscle pain, and postural hypotension**.**

→**Cushing's syndrome:** it is characterized by hypersecrection of glucocorticoids and usually caused by a tumor of the adrenal cortex.



→Salt & water retention, edema, hypokalemia, ↑ HT, obesity.

→Peptic ulcer disease and GIT ulcerations.

→Osteoporosis.

→Diabetes mellitus.

→Viral and fungal infections.

→Delayed wound healing, skin atrophy, and myopathy.

→Suppression of growth in children.

→Cataract...

➢ Strategies in the use of glucocorticoids:

- Use a short or intermediate acting steroid.

- Use the minimal possible dose.

- 2/3rds of the dose in morning and 1/3rd in evening.

- Use alternate day therapy which is associated with less suppression to growth of children, less suppression of the hypothalamic-pituitary-adrenal axis, and fewer side effects.

"نحن ندفن في الطب أعواما تحت التراب, حتى نصبح يوما أشجارا مثمرة فوق التراب"

Good luck