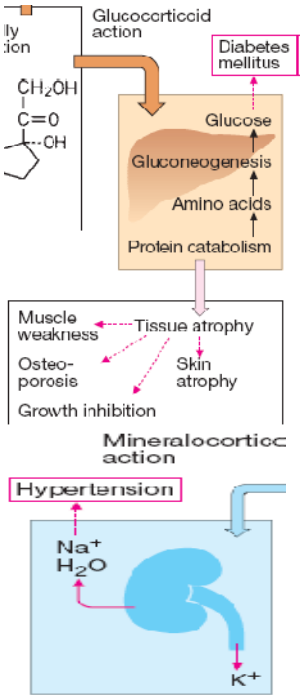
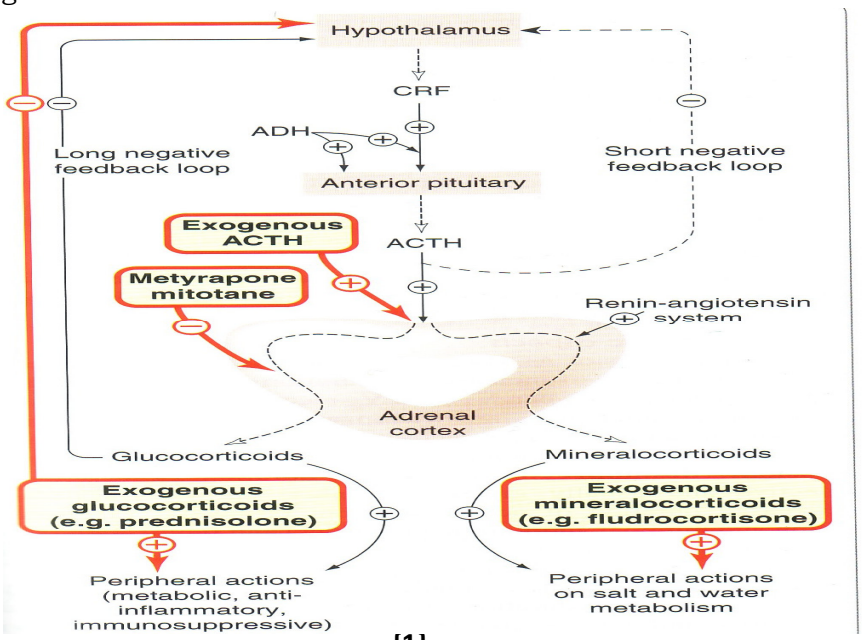
- The principal adrenal steroids are mineralocorticoids, glucocorticoids & sex hormones.
- Main endogenous GC are hydrocortisone ,corticosterone , affect carbohydrate & protein metabolism & have anti-inflammatory & immunosuppressive action.
- Main endogenous mineralocorticoid is aldosterone, affects water electrolyte balance.
- A deficiency in corticosteroids [Addison's disease] is characterized by muscle weakness, low BP, depression, loss of weight, hypoglycaemia.
- Excessive production of glucocoticoids is called Cushing's syndrome.
- Excessive production of mineralocorticoids is called Conn's syndrome.



SYNTHESIS & RELEASE:

- The starting substance for synthesis is cholesterol.
- The first step in the synthesis is regulated by ACTH , is the rate- limiting step.
- Metyrapone prevents the β-hydroxylation at C11 , used to test ACTH production , in Cushing's syndrome.
- Trilostane , ↓ 3β-dehydrogenase , used in Cushing's syndrome & primary hyperaldosteronism.
- Aminoglutethimide & ketoconazole.



Glucocortiods

Drugs used: Hydrocorisone, Prednisolone & Dexamethasone.

❖ Metabolic actions :

- **On carbohydrates**: decreased uptake and utilisation of glucose and increased gluconeogenesis; this causes a tendency to hyperglycaemia.
- **On proteins**: increased catabolism, reduced anabolism.
- **On fat**: a permissive effect on lipolytic hormones, and a redistribution of fat, as in Cushing's syndrome.

❖ Regulatory actions :

- **On hypothalamus and anterior pituitary**: a negative feedback action resulting in reduced release of endogenous glucocorticoids. The suppress pituitary release of ACTH, GH ,TSH &LH
  - ✓ They promote fat redistribution

- **On vascular events**: reduced vasodilatation, decreased fluid exudation.

- **On cellular events:**
  - *in areas of acute inflammation:* decreased influx and activity of leucocytes.
  - *in areas of chronic inflammation*: decreased activity of mononuclear cells, decreased proliferation of blood vessels, less fibrosis.
  - *in lymphoid areas*: decreased clonal expansion of T and B cells and decreased action of cytokine-secreting T cells.
  - *On inflammatory and immune mediators*:
    - Glucocorticoids inhibit the function of tissue macrophage & other antigen- presenting cells.
    - decreased production and action of cytokines including many interleukins, tumour necrosis factor-γ, granulocyte-macrophage colony-stimulating factor
    - reduced generation of eicosanoids
    - decreased generation of IgG
    - decrease in complement components in the blood.

- ***Overall effects:*** reduction in chronic inflammation and autoimmune reactions but also decreased healing and diminution in the protective aspects of the inflammatory response.

❖ Catabolic & Anti-anabolic effect:

- Although they stimulate protein synthesis in the liver , they have catabolic effect in lymphoid,Connective tissue, muscle, fat& skin.
- Catabolic effect on the bone → osteoporosis.

❖ Increase resistance to stress :

- ↑ plasma glucose level provide body with energy
- Modest rise in blood pressure by enhancing the vasoconstriction effect of adrenergic stimuli on small vessel

❖ Alter blood cell level in plasma:

- Glucocorticoids ↓ in eosinphil, basophil, monocytes & lymphocytes
- They increase hemoglobin , erythrocytes & polymorphnuclear leukocyte.

MECHANISM OF ACTION OF THE GLUCOCORICOIDS:

- Glucocorticoids interact with intracellular receptors; the resulting steroid-receptor complexes dimerise (form pairs) then interact with DNA to modify gene transcription : inducing synthesis of some proteins & inhibiting the synthesis of others.

- For metabolic action , most mediator proteins are enzymes ,e.g. cAMP-dependant Kinase, but not all action on gene are known.

- For anti- inflammatory & immunosuppressive actions, some action at the level of the gene are known :

  A. Inhibition of transcription of the gene for cyclooxygenase-2, cytokines (e.g. the interleukins), cell adhesion molecule & the inducible form of nitric oxide synthase.
  B. Block of vitamin. D_3- mediate induction of osteocalcin gene in the osteoblast & modification of transcription of the collagenase genes.
  C. Increase synthesis of annexin-1 which is important in negative feedback on hypothalamus & anterior pituitary & may have anti-inflammatory actions .

- Some non-genomic (rapid) effects of glucocorticoids have also been observed.

PHARMACOKINETICS:

- Administration can be oral, topical and parenteral(IV , IM) rapidly & completely absorbed .
- The drugs are bound to corticosteroid-binding globulin (CBG) in the blood and enter cells by diffusion.{ the remainder is bound to albumin}
- The metabolites are conjugated to glucuronic acid or sulfate & excreted by the kidney.
- When prolonged use of systemic glucocorticoids is necessary, therapy on alternate days may decrease the unwanted effects.
- Hydrocortisone has a plasma half-life of 90 minutes, biological effects occur after 2-8 hours. Inactivated by the reduction of the double bond between C4 and C5.
- This occurs in liver cells and elsewhere.
- Cortisone and prednisone are inactive until converted in vivo to hydrocortisone and prednisolone , respectively.

ADVERSE EFFECTS:

- Unwanted effects are seen mainly with prolonged systemic use as anti-inflammatory or immunosuppressive agents (in which case all the metabolic actions are unwanted), but not usually with replacement therapy.
- **The most important are:-**

  ☒ suppression of response to infection
  ☒ suppression of endogenous glucocorticoid synthesis
  ☒ metabolic actions
  ☒ Osteoporosis
  ☒ peptic ulcers
  ☒ acute psychosis
  ☒ Cataracts
  ☒ Increased intraocular pressure
  ☒ iatrogenic Cushing's syndrome

DEXAMETHASONE SUPPRESSION TEST:

- Dexamethasone suppression test measures the response of the adrenal glands to ACTH . Dexamethasone is given and levels of cortisol are measured. Cortisol levels should decrease in response to the administration of dexamethasone.

- There are two different types of dexamethasone suppression tests: the low-dose test and the high-dose test.

- If there is not a normal response on the low-dose test, abnormal secretion of cortisol is likely (Cushing's Syndrome).

- This could be a result of a cortisol-producing adrenal tumor, a pituitary tumor that produces ACTH, or a tumor in the body that inappropriately produces ACTH.

- The high-dose test can help distinguish a pituitary cause (Cushing's Disease) from the others.

Adrenocortical Insufficiency:

A. If it is chronic called (Addison's Disease):

- caused by adrenal cortex dysfunction, lack of patient response to corticotrophin

- about 20–30 mg of hydrocortisone must be given daily, with increased amounts during periods of stress. {2/3 of the dose in the morning &1/3 in the afternoon}

- Could be supplemented by an appropriate amount of fludrocortisone

- Betamethasone: has a mineralocorticoid activity 20 times than normal.

B. Acute adrenal insufficiency:

- Therapy consists of correction of fluid and electrolyte abnormalities and treatment of precipitating factors in addition to large amounts of parenteral hydrocortisone.

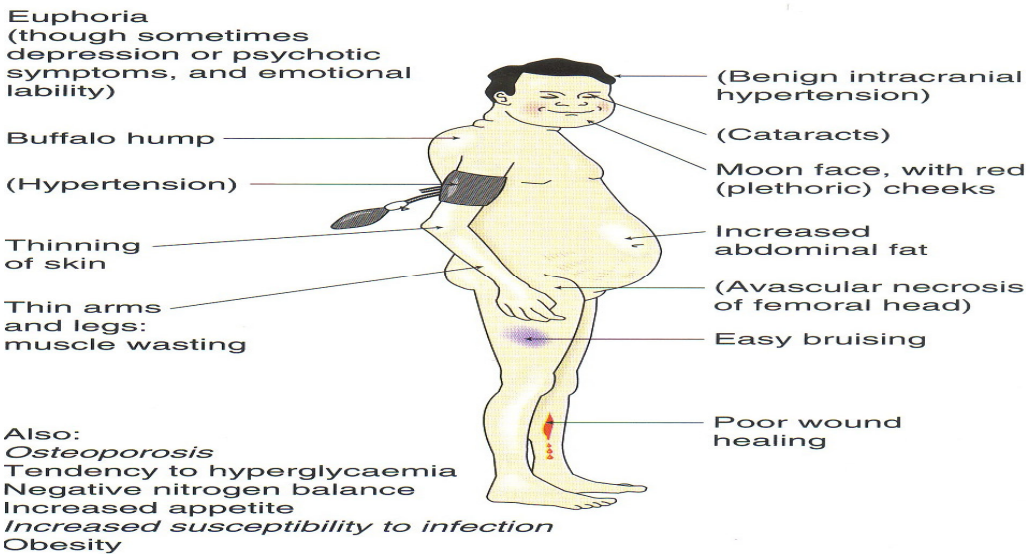
- Mineralocortocoid is also given

Cushing's Syndrome

- It is characterized by hypersecretion of glucocorticoides due to either excessive release of corticotrophin by the ant.pituitary by an adrenal tumor.

- is treated by surgical removal of the tumor producing ACTH or cortisol, irradiation of the pituitary tumor, or resection of one or both adrenals.

- These patients must receive large doses of cortisol during and following the surgical procedure.



- Stimulation of Lung Maturation in the Fetus

- Lung maturation in the fetus is regulated by the fetal secretion of cortisol.

- Treatment of the mother with large doses of glucocorticoid reduces the incidence of respiratory distress syndrome in infants delivered prematurely.

- Betamethasone is chosen because maternal protein binding and placental metabolism of this corticosteroid is less than that of cortisol

CLINICAL USES:

1. Replacement therapy for patients with adrenal failure (Addison's disease).

2. Anti-inflammatory/immunosuppressive therapy { as in rheumatoid arthritis & osteoarthritis }

3. Glucocorticoids are useful in the treatment of symptom of drug, serum transfusion .
4. in asthma

5. topically in various inflammatory conditions of skin, eye, ear or nose (e.g. eczema, allergic conjunctivitis or rhinitis)

6. in hypersensitivity states (e.g. severe allergic reactions)

7. in miscellaneous diseases with autoimmune and inflammatory components (e.g. rheumatoid arthritis and other 'connective tissue' diseases, inflammatory bowel diseases, some forms of haemolytic anaemia, idiopathic thrombocytopenic purpura)

8. to prevent graft-versus-host disease following organ or bone marrow transplantation.

9. In neoplastic disease:

   - in combination with cytotoxic drugs in treatment of specific malignancies (e.g. Hodgkin's disease, acute lymphocytic leukaemia)
   - to reduce cerebral oedema in patients with metastatic or primary brain tumours and in the postoperative period (dexamethasone is the drug used)
   - as a component of antiemetic treatment in conjunction with chemotherapy.

PRECAUTION:

- Patients receiving glucorticoids must be monitored carefully for the development of:-
  - ✓ hyperglycemia,
  - ✓ glycosuria,
  - ✓ sodium retention with edema or hypertension,
  - ✓ hypokalemia,
  - ✓ peptic ulcer,
  - ✓ osteoporosis,
  - ✓ and hidden infections

CONTRAINDICATION:

- peptic ulcer,
- heart disease or hypertension with heart failure,
- certain infectious illnesses such as varicella and tuberculosis,
- psychoses,
- diabetes mellitus,
- osteoporosis,
- glaucoma.

Mineralocorticoids

Aldosterone:

- It is synthesized mainly in the zona glomerulosa of the adrenal cortex.
- ACTH & angiotensin stimulate the release of aldosterone.
- Aldosterone promote the reabsorption of Na^+ from the distal convoluted tubule & cortical collecting tubules, loosely coupled to the excretion of K^+ & H^+.
- Mineralocorticoids lead to: hypernatremia, hypokalemia, metabolic alkalosis, increase plasma volume & hypertension.
- Mineralcorticoids acts by binding to mineralcorticoid receptor in the cytoplasm of target cells especially principal cells of the distal convoluted tubule &collecting tubule in the kidney .the drug receptor complex activates a series of event similar to those described for glucocorticoids.
- Hyperaldosteronism is treated with spironolactone .

Deoxycorticosterone:

- It is the precursor of aldosterone.
- Its secretion is primary under the control of ACTH.

Fludrocortisone:

- It is a potent steroid.
- It is widely used for its mineralocorticoids activity
- It is used in the treatment of adrenocortical insufficiency associated with mineralcorticoid deficiency.
- has glucocorticoid and mineralocorticoid activity.

- Mineralocorticoids
- Fludrocortisone is given orally to produce a mineralocorticoid effect. This agent:

1. increases Na^+ reabsorption in distal tubules and increases K^+ and H^+ efflux into the tubules
2. acts, like most steroids, on intracellular receptors that modulate DNA transcription causing synthesis of protein mediators
3. is used with a glucocorticoid in replacement therapy.

Adrenal androgens

"Antagonist of adrenocortical agent"

A. Synthesis inhibitors & glucocorticoid antagonist:

1. Ketoconazole:

- it is antifungal agent, strongly inhibit all gonadal & adrenal steroid hormone synthesis.
- It is used in the treatment of cushing's syndrome.
- It is hepatotoxic drug.

2. Mifepristone:

- It is a potent glucocorticoid receptor antagonist as well as anti progestin.
- It forms a complex with the glucocorticoid receptor, but the rapid dissociation of the drug from the receptor → faulty translocation into the nucleus.
- It used for inoperable patients with ectopic ACTH secretion or adrenal carcinoma who have failed to respond to other therapy.
- Used as a contraceptive method (now).

B. Mineralocorticoid inhibitors:

1. Spironolactone :

- Spironolactone competes for the mineralocorticoid receptor and thus inhibits sodium reabsorption in the kidney
- It can also antagonize aldosterone and testosterone synthesis.
- It is effective against hyperaldosteronism.
- The drug is also useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle.

سبحانك اللهم وبحمدك

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THE END