Adrenocorticosteroids

The adrenal cortex secretes: -

1. Glucocorticoids (cortisol).

2. Mineralocorticoids (aldosterone).

3. Androgenic or estrogenic activity: Dehydroepiandrosterone (DHEA) sulfate and androstenedione, respectively.

Glucocorticosteroids (Cortisol)

- Endogenous substances.

- Very great in physiologic levels.

- Between 10-20% of expressed genes in a cell are regulated by glucocorticoids (almost 20% of the body functions are affected by cortisol).

- They have a huge clinical use (we use them in almost every disease).

- Glucocorticosteroids effects are strongly linked with their side effects. This means when they are used, their side effects are very common. For example, 90% of the patients are going to have **hypertension** (elevated blood pressure, not chronic hypertension), 80% are going to have **hyperglycemia** and if we continue using them 30% of the hyperglycemic patients will end up having diabetes mellitus, 30 – 40 % will have **psychotic issues or depression**.

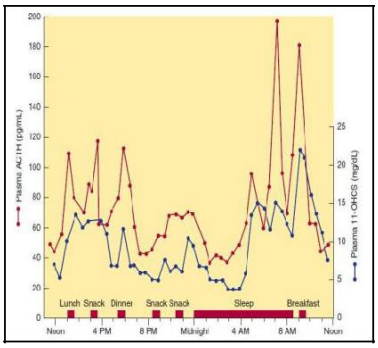
  <u>Why do we use these drugs even if they have this strong link between the effect and the side effect?</u>

  We will answer this question by an example, a patient has idiopathic thrombocytopenia, which means the level of the platelets in patient's blood is decreasing, they only way to treat him is giving him cortisol.

  Another example for better understanding, sometimes we can't treat urticaria (allergy toward allergic materials) unless we use corticosteroids.

So, we can use cortisol on daily basis even if it has these life-threatening side effects, but we have to know these side effects very well so we can manage them.

- Cortisol get secreted between 4AM – 8AM in the morning, that's why we dose our patient at 9AM or early in the morning to mimic the physiological cycle of cortisol.

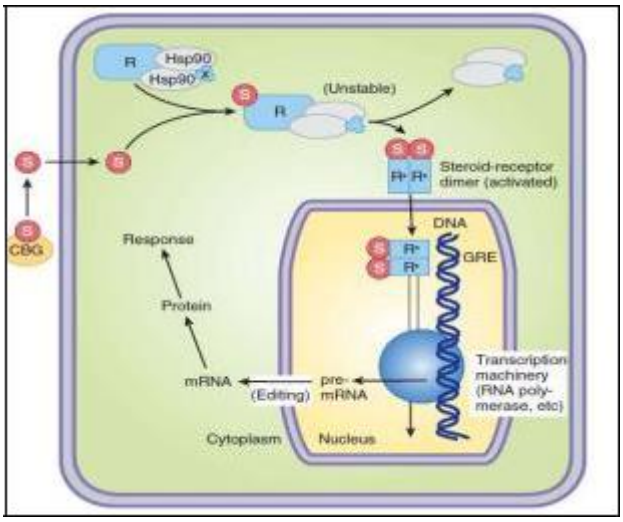


- **The effect of glucocorticosteroids:**

  As we said glucocorticosteroids affect the expression of almost 20% of our genes, but how does that happen?
  glucocorticosteroids are intracellular drugs (just like the growth hormone), but in different tissues they produce different effect, this happens because of the **receptor tissue specific activity**, which means according to the type of tissue the activity will be different.

- **The mechanism of action of glucocorticosteroids:**

  Glucocorticosteroid (cortisol) crosses the membrane of a cell, then it binds with the **glucocorticosteroid receptor (GR)** which is bound to HSP90 and HSP70 already, this complex (glucocorticosteroid + GR + HSP90/70) is unstable, so before it can go to the nucleus, HSP90 and HSP70 unbind from the complex and the glucocorticosteroid with its receptor goes all the way to the nucleus. In the nucleus the glucocorticosteroid will work as co-expresser or co-suppresser (activation or inhibition to gene expression respectively), so according to the tissue the glucocorticosteroid is going to work as activator or inhibitor for mRNA expression. For example, in the liver if gluconeogenesis is taking place cortisol is going to <u>activate</u> the expression of glucagon. Another example in the lymphocytes, cortisol will <u>inhibit</u> the expression of IL1, IL2, TNFα and IF-γ.



- Glucocorticoids control a lot of transcription factors that play a role in regulation of growth factors and proinflammatory cytokines, and to a greater extent, mediate antigrowth, anti-inflammatory and immunosuppressive effects of glucocorticoids.

- **Permissive actions of glucocorticoids** (In the absence of glucocorticoids, these functions become deficient): -

    1. The response of vascular and bronchial smooth muscle to catecholamines is diminished in the absence of cortisol and is restored by physiological amounts of it.

       What about if we increased Glucocorticoids level?
       The sensitization will increase just like the thyroid hormones (T3, T4), so the adrenaline and noradrenaline receptors (α and β) will be sensitized. This is the first side effect that appears in the increased level of glucocorticoids (pharmacological level) which is **hypertension**.

    2. Lipolytic responses of fat cells to catecholamines, ACTH and GH are attenuated in the absence of glucocorticoids.

    3. In the absence of cortisol, glomerular filtration is impaired, vasopressin (ADH) secretion is augmented and the ability to excrete water load is abolished.

- **Dose-dependant Actions of glucocorticoids**

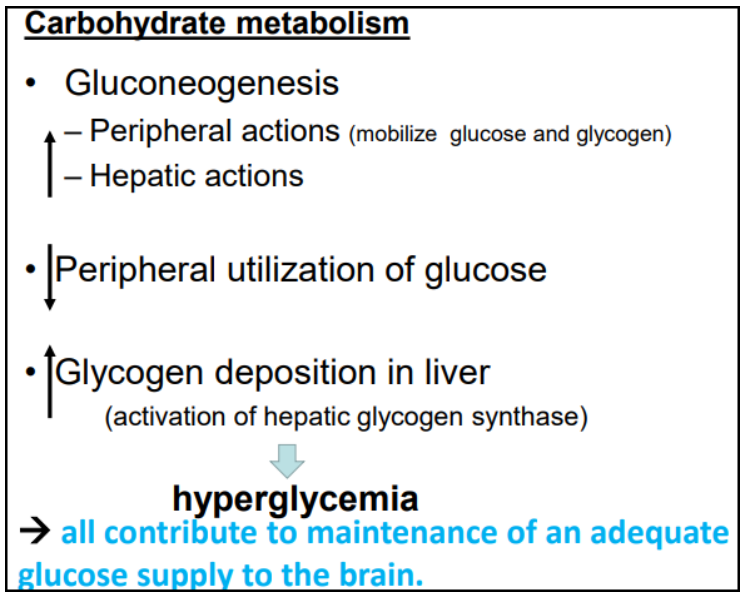
  This is very important in pharmacology because we dose the patients, and in many cases we use high doses because there is no other way to treat them. For example, in autoimmune diseases or in high allergic reaction.

  A. Metabolic effects:

    1. Stimulate gluconeogenesis and glycogen synthesis in the fasting state.

       As we said, what stimulates the secretion of cortisol is hypoglycemia and stress, by that the brain starts needing more glucose, so gluconeogenesis starts in order to supply the brain with glucose, gluconeogenesis is the process of making glucose from amino acids (muscle) or glycerol (adipose tissue). Glycogen is also synthesized by the effect of cortisol because the liver has β1 and β2

receptors which are going to be affected by the increased amount of cortisol (sensitized adrenergic receptors on the liver) that's why the glycogen gets produced to keep up with the demand of adrenaline. Glycogenesis process (glycogen synthesis) needs glucose to work, so gluconeogenesis has to happen. It's a cycle: amino acids and glycerol → gluconeogenesis → glucose → liver → glycogenesis → glycogen. The end result of this cycle is **hyperglycemia**.



2. Stimulate the release of amino acid during muscles catabolism (muscle weakness or atrophy).

3. Increase serum glucose levels and thus insulin release.

4. Inhibit glucose uptake by muscles (insulin resistance), with time this will lead to diabetes mellitus type 2 (hyperinsulinemia and hyperglycemia).

5. Stimulate lipase and thus lipolysis.

- The increase in insulin stimulates lipogenesis and to a lesser degree lipolysis is inhibited → leading to a net

increase in deposition of fat, combined with increased release of fatty acids and glycerol into the circulation. This explains the redistribution of fat in the patients (**buffalo hump and moon face**).

B. Catabolic effects:

Although glucocorticoids increase protein and RNA synthesis in the liver, they have catabolic and antianabolic effects in lymphoid and connective tissue, muscle, peripheral fat and skin, leading to:

1. Decreased muscle mass → weakness.
2. Thinning of the skin.
3. Osteoporosis.
4. Reduced growth in children (growth retardation).

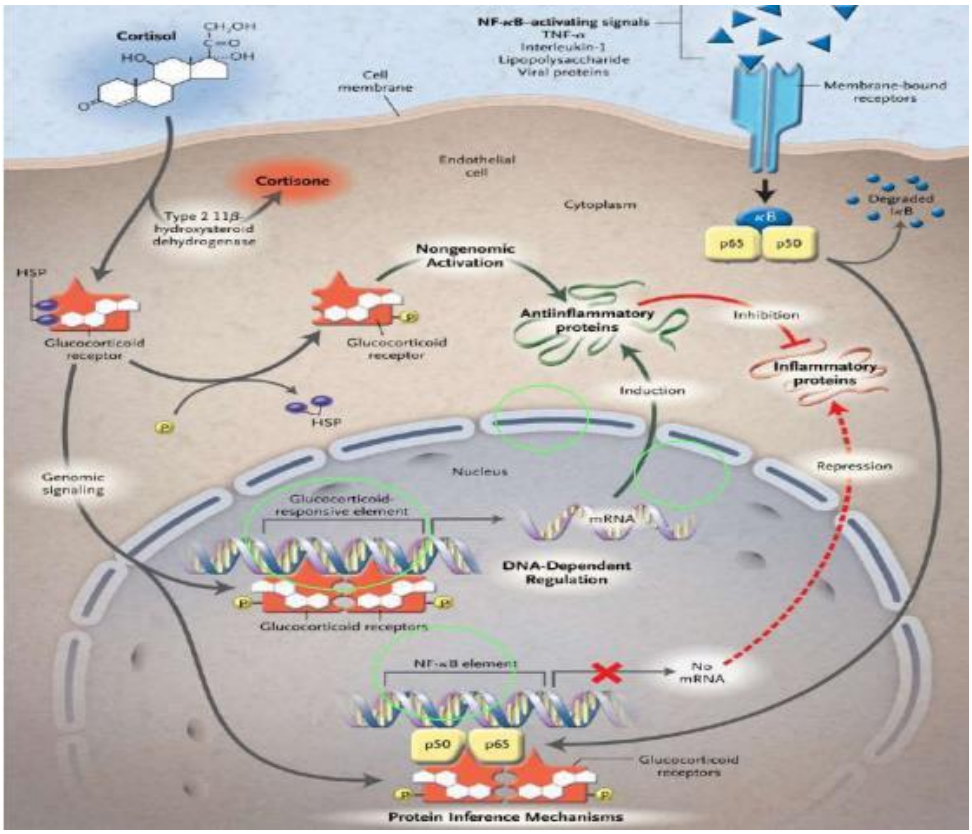
- By far the side effects of glucocorticosteroids that we took are: Hypertension, hyperglycemia, decreased muscle mass, thinning of the skin, osteoporosis, reduced growth in children, buffalo hump and moon face. These side effects happen with the long-term use of glucocorticosteroids (pharmacological dose) and only when they are given orally or by injection (in high doses). For example the inhalers of glucocorticosteroids don't lead to these side effects because the dose is low.

C. Anti-inflammatory and immunosuppressive effects: (there is no drug better than glucocorticosteroids in these effects)

1. Glucocorticoids dramatically reduce the manifestations of inflammation. Why?

   The proposed mechanism of glucocorticosteroids in anti-inflammatory effect is: the cortisol enters inside the cell and bind to the glucocorticoid receptor (GR) which goes to the **genomic** signaling and then goes to the gene inside the nucleus, this gene is responsible for expressing the mRNA for the inflammatory proteins (IL1, IL2, IL6,

IL17, TNFα and IF-γ) the glucocorticoid receptor inhibits the expression of this gene, and by that the inflammation is reduced. This mechanism takes time, so there is a faster **nongenomic** way, the same glucocorticoid receptor that works in the genomic mechanism does not enter the nucleus, instead it activates the anti-inflammatory proteins directly, and they inhibit the inflammation proteins and this reduces the inflammation. In addition, the expression of lipocortin which is an anti-inflammatory protein is increased.



2. The inflammatory proteins have other jobs besides the inflammation, which are the proliferation and migration of immune cells, so when glucocorticosteroids are used, the inflammation or the migration and proliferation of immune cells (lymphocytes, macrocytes and antigen presenting cells) are reduced. So that's why the glucocorticosteroids are very useful in the anti-inflammatory, immunosuppressive and antiallergic effects.

3. The problem in these effects is that the patient loses the immunity, so the patient will be immunocompromised. For example, if the patient has latent TB, after using glucocorticosteroids he can develop tuberculosis. Another example is that when you are stressed from studying or whatever the reason is, cortisol level is high so the anti-inflammatory effects are high, so your immunity will be weak and you start to become sick because there is high chance for the latent things either viral, bacterial or fungal to affect you.

4. Inhibit phospholipase A2, and thus synthesis of prostaglandins, leukotrienes and platelet activating factor, thus influencing the inflammatory response.

5. Reduce expression of cyclooxygenase-2, the inducible form, during inflammatory reactions.

6. Reduces mast cell degranulation and histamine release, this is very important because every inflammation is connected with mast cells and histamine.

7. Reduces antibody production at large doses but not affected by moderate dosage, that's why we use high doses in treating idiopathic thrombocytopenia and ulcerative colitis because we want to reduce the allergic reaction in them.

D. Other effects:

1. Adrenal insufficiency causes marked slowing of the alpha rhythm of the EEG and is associated with depression.

2. Increased amounts of glucocorticoids often produce behavioral disturbances: initially insomnia and euphoria and subsequently depression. Euphoria and insomnia

because too much adrenaline activity is taking place, however subsequently depression is caused by the increase of adrenaline which disturbs the balance between adrenaline, serotonin and dopamine, which will cause depression, mood changes, psychosis and may cause mania, these side effects usually happen in the long-term usage.

3. Large doses of glucocorticoids may increase intracranial pressure because of increased hypertension (pseudotumor cerebri).

4. Glucocorticoids given chronically suppress the pituitary release of ACTH, growth hormone, thyroid-stimulating hormone, and luteinizing hormone. So, if given more than 21 days (3 weeks) they will suppress the release of ACTH and many other things, including the glucocorticosterids, so the patient will be dependent on the drug which will lead to adrenal atrophy. In contrast, sudden withdrawal of the drug will cause adrenal crisis because the permissive effect isn't working, so we have to do tapering of the drug after 21 days from giving it.

5. Peptic ulceration, possibly by suppressing:
    a) Prostaglandin synthesis.
    b) Immune response against Helicobacter pylori.

6. Antagonizes the effects of vitamin D on Ca2+ absorption, that's why osteoporosis is a side effect.

7. Increases the number of platelets and RBCs.

8. Development of fetal lung and formation of surfactant.

- **Synthetic Corticosteroids:**

A. **Short to medium-acting glucocorticoids**: high selectivity toward glucocorticoid receptors and low activity toward aldosterone receptors, so with long term use edema around the stomach will be formed (another side effect).

1. Cortisone: oral.
2. Prednisone: oral.
3. Prednisolone: oral, injectable and topical.
4. Methylprednisolone: oral, injectable and topical.

B. **Intermediate-acting glucocorticoids** (not important)

C. **Long- acting glucocorticoids**

1. Betamethasone (famous in Jordan).
2. Dexamethasone: available forms: oral, injectable and topical.

   Very potent anti-inflammatory activity, stronger than Prednisolone and has no activity in salt retention. This makes it very commonly used especially in treating idiopathic thrombocytopenia and cancer (against the proliferation of immune cells). It is usually not used in the normal cases because it has much more side effects than Prednisolone (side effects are profound). For example dexamethasone is used in treating childhood acute lymphocytic leukemia, it is given in long term use, and the patients always have to be scanned by CT and MRI because dexamethasone is linked with vascular necrosis which leads to insufficient blood supply to the bones especially the hip bones. It is also used in patients that have exacerbation of asthma, it is given in short term use (we use decadrone in this case; a form of dexamethasone).

D. **Mineralocorticoids**: weak with inflammation but strong in salt retention, which means they have an activity on

glucocorticoids receptors but it has much stronger activity on the aldosterone receptors.

1. Fludrocotisone.

- Therapeutic Uses of glucocorticoids:

1. **Cushing's syndrome:**

   - Cushing's syndrome is the result of bilateral adrenal hyperplasia secondary to an ACTH secreting pituitary adenoma (Cushing's disease), and occasionally is due to tumors or nodular hyperplasia of the adrenal gland or ectopic production of ACTH by other tumors. (ACTH → excess glucocorticoids).

   - Replacement therapy with large doses of hydrocortisone following surgical treatment of Cushing's syndrome.

2. **Primary generalized glucocorticoid resistance (Chrousos syndrome)**: A rare, genetic condition due to inactivating mutations of the glucocorticoid receptor gene.

   - It is associated with increased production of ACTH leading to high circulating levels of cortisol and cortisol precursors such as corticosterone and 11-deoxycorticosterone with mineralocorticoid activity, as well as of adrenal androgens.

   - Therapy of this syndrome is high doses of synthetic glucocorticoids such as dexamethasone with no inherent mineralocorticoid activity (inhibition of ACTH).

3. **Stimulation of lung maturation in the fetus** by administration of **betamethasone** to the mother when premature delivery is anticipated → reduce incidence of respiratory distress syndrome (RDS), which means we reduce the possibility of immature lungs in the premature baby by giving him glucocorticoids because they increase the surfactant activity of the alveoli and assure the maturation of the lungs.

Betamethasone is given here to the mother only in the last months of pregnancy, (it is contraindicated in the first three months because it may cause teratogenic activity).

4. **Treatment of Non-adrenal disorders:**

    - Due to anti-inflammatory and immunosuppressive functions, and ability to alter leukocyte function.

    - Corticosteroids are not usually curative; thus, the pathologic process may progress while clinical manifestations are suppressed.

Glucocorticoids:

These drugs have very wide therapeutic uses in both adrenal and non-adrenal disorders, continuing with the last lecture these are some indications for theirNon Adrenal disorders use:

1. **Inflammatory conditions of the bones and joints:**
    a. Arthritis
    b. Bursitis
    c. Tenosynovitis
2. **Neurological Disorders:**
    a. Cerebral Edema
    b. Multiple Sclerosis
3. **Organ Transplants:** Used as immunosuppressants to decrease the probability of rejection of the organ.
4. **Pulmonary Diseases:**
    a. Aspiration Pneumonia
    b. Bronchial Asthma
    c. Sarcoidosis
    d. Used in the prevention of Infant Respiratory Distress Syndrome (IRDS)
5. **Renal Disorders:** Such as Nephrotic Syndrome
6. **Skin Diseases:** Such as Atopic Dermatitis
7. **Thyroid Diseases**

TABLE 39–2 Some therapeutic indications for the use of glucocorticoids in nonadrenal disorders.

Disorder	Examples
Allergic reactions	Angioneurotic edema, asthma, bee stings, contact dermatitis, drug reactions, allergic rhinitis, serum sickness, urticaria
Collagen-vascular disorders	Giant cell arteritis, lupus erythematosus, mixed connective tissue syndromes, polymyositis, polymyalgia rheumatica, rheumatoid arthritis, temporal arteritis
Eye diseases	Acute uveitis, allergic conjunctivitis, choroiditis, optic neuritis
Gastrointestinal diseases	Inflammatory bowel disease, nontropical sprue, subacute hepatic necrosis
Hematologic disorders	Acquired hemolytic anemia, acute allergic purpura, leukemia, lymphoma, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, multiple myeloma
Systemic inflammation	Acute respiratory distress syndrome (sustained therapy with moderate dosage accelerates recovery and decreases mortality)
Infections	Acute respiratory distress syndrome, sepsis
Inflammatory conditions of bones and joints	Arthritis, bursitis, tenosynovitis
Neurologic disorders	Cerebral edema (large doses of dexamethasone are given to patients following brain surgery to minimize cerebral edema in the postoperative period), multiple sclerosis
Organ transplants	Prevention and treatment of rejection (immunosuppression)
Pulmonary diseases	Aspiration pneumonia, bronchial asthma, prevention of infant respiratory distress syndrome, sarcoidosis
Renal disorders	Nephrotic syndrome
Skin diseases	Atopic dermatitis, dermatoses, lichen simplex chronicus (localized neurodermatitis), mycosis fungoides, pemphigus, seborrheic dermatitis, xerosis
Thyroid diseases	Malignant exophthalmos, subacute thyroiditis
Miscellaneous	Hypercalcemia, mountain sickness

31

Note: The diseases above are not for memorization they just show the wide therapeutic uses of these drugsand at the same time wide side effects which called (systemic side effect) except in inhalation or topical dosage form.

Allergies:

Any type of allergic reaction with disregard to the causative agent responds adequately to Glucocorticoids. In an allergic reaction one of two things may occur:

1. Mast cells release histamine

2. Antibodies are formed, therefore, Autoimmune diseases can also be treated with Glucocorticoids

Examples of allergic reactions are:

1. Angioneurotic Edema (Dr. Malik said this isn't important)
2. Asthma
3. Bee Stings
4. Contact Dermatitis
5. Drug Reactions
6. Serum sickness
7. Allergic Rhinitis
8. Urticaria

As you may have noticed in all the previous examples of allergic reactions they all have either of the two mechanisms stated previously which are involved in the occurrence of an allergic reaction (Histamine and Antibodies). Thus, the method of action of Glucocorticoids in allergic reactions is through inhibiting the release of histamines or the production of antibodies. Since these drugs inhibit the formation of antibodies by the immune system, they **can be used in any disease**

whose pathogenesis relies mainly on the production of antibodies (mainly autoimmune diseases).

It is very important to know that the Glucocorticoids should be stopped after the 6 weeks as they have many unwanted side effects such as:

1. Hypertension
2. Hyperglycemia
3. Diabetes
4. Psychosis
5. Depression

Summary of Glucocorticosteroids:

They are **used for the treatment of**:

1. Primary and Secondary Adrenal Disorders such as:

Adrenal Insufficiency

Hyperplasia of the Adrenal Glands

ACTH secreting Adenoma of the Pituitary

2. Almost all other disease affecting the body, amazingly can even be used in sepsis(infection)

Adverse effects:

- Affect every part of the body
- Major cause of Iatrogenic Cushing's Syndrome after 2 or 3*weeks of usage. (*new guidelines said 21 days)
- Metabolic Effects
    a. Breakdown of proteins lead to muscle wasting and decreased muscle mass

High gluconeogenesis leads to Hyperglycemia which can turn into Diabetes Mellitus Type 2 with Hyperinsulinemia and Insulin Resistance of the peripheral tissues.

*(If your diabeticpatientwho was taken exogenous insulin doesn't respond to itafter atimethis is related to insulin resistance which glucocorticoids'highconcentration is one of its causes– maybe the patient take cortisone or he has hyper cortisol in his body -)

Rule : the 2nd misused drug in the word after antibiotic is glucocorticoid

- Redistribution of fat
- Osteoporosis
- Wound healing impairment;in the wound there is migration of lymphocytes +process called angiogenesis (the formation of new blood vessels from pre-existing blood vessels), and there is involvement of inflammations , chronic exposure to excess glucocorticoids will reduce angiogenesis and inflammatory mediators of healing. (Corticosteroids have an inhibitory effect on macrophages, leading to a decline in collagen synthesis).

Also for diabetic patient who take cortisone, they have two problems; 1st they already haveno perfusion to the periphery because of blocking the vessels that supply it , 2nd glucocorticoidswill inhibit the migration of leukocyte ,lymphocyte ….

- Peptic and stress ulcers
- Masking of Mycotic and Bacterial infections (so the patientwill haveinfection but it does not appear and we don't know about it because the drug will inhibit the signs of inflammation)
- Severe Myopathy
- CNS effects including Psychosis , Depression ,hypomania ,insomnia, and increase appetites
- Increased intraocular pressure known as Glaucoma (allglucocorticoids increase the intraocular pressure)
- Benign Intracranial Hypertension (pseudotumorcerebri), also may occur with Growth Hormone therapy

- Growth retardation in Children
- If the Glucocorticoid being taken affects the Aldosterone pathway (like the drugs we mentioned in the last lecture in the tablethathave salt retention effect likeprednisone and methylprednisolonebut dexamethasone can't do this because it has zero effect on salt retention) whenglucocorticoids bind to Na/k/H pumpon the collective duct , it may cause retention of Sodium and Water and excessive excretion of Potassium and H+ leading to Hypokalemia (lose of K+) and Alkalosis(lose of H+) , the opposite happen if I inhibit the pump we will have Hyperkalemia acidosis

15. Hypertension in patients with normal Cardiovascular and Renal functions with long term usage (explained in the lastlecture how that happen)
16. Edema and hypoproteinemia in patients with Renal Disease

- Congestive Heart Failure in patients with Cardiovascular diseases
- Suppression of the Hypothalamic-Pituitary-Adrenal Axis which may lead to adrenal insufficiency:

1. This occurs following their use for more than 2 or 3 weeks
2. If these drugs are to be stopped, they cannot be stopped abruptly and need to be tapered.
3. After tapering the dose and stopping the Glucocorticoids completely it may take from 2-12 months for the axis to start functioning normally again, and a further 6-9 months for the Cortisol level to go back within normal ranges.
4. The longer the time of therapy, the more time needed for the axis to return to normaland more difficult to treatadrenalsuppression
5. In this case treatment of the patients with ACTH has no effect on decreasing the time needed to return to normal function.
6. Tapering the dose is beneficial as it prevents the occurrence of Acute Hypoadrenalism (which may be fatal

Contraindications:

1. Peptic ulcers
2. Heart Disease
3. Hypertension with Heart Failure
4. Diabetes Mellitus
5. Certain infections like TB and Varicella
6. Psychosis
7. Glaucoma
8. Osteoporosis

It is not absolute contraindication it is relatively contraindication (for examplehypertensionpatient without heart failure we can use it for short term while taking care to the hypertensions that he already has ,anther example , patient with diabetesMellitus and he have persists cough also here we can use glucocorticoids for 4-5 days or maximum for one week but with monitoring glucose level)

Note: The most misused drugs following antibiotics are Glucocorticoids.

Mineralocorticoids:

Used in the treatment of Adrenocortical Insufficiency associated with Mineralocorticoid Deficiency.

Can be divided into:

1. Natural such as:

1. **Aldosterone** (mainly under the regulation of Angiotensin 2 and is only partially regulated by ACTH)
2. **Deoxycorticosterone**

B. Synthetic: **Fludrocortisone** (most commonly prescribed salt retaining hormone due to its high potency (remember 250 from the table) and a mix of both Glucocorticoid and Mineralocorticoid activities)

The previous hormones are mainly used in salt retention by:

1. Promoting the reabsorption of Sodium from the distal part of the Distal Convoluted Tubule and the Cortical Collecting Tubules and in turn stimulating the excretion of Potassium and Hydrogen Ions (H+).
2. Promoting the reabsorption of sodium in Sweat and Salivary Glands, the Gastrointestinal Mucosa, and across cell membranes

In the case of a functional tumor releasing high levels of Aldosterone or over dosage with Mineral Corticoids, the following effects occur:

1. Hypokalemia
2. Metabolic Alkalosis
3. Increased plasma volume
4. Hypertension

B Fludrocortisone is the most commonly prescribed salt retaining hormone. **It is a potent steroid with both glucocorticoid and mineralocorticoid activity.**

X Mineralocorticoids are indicated in the treatment of adrenocortical insufficiency associated with mineralocorticoid deficiency