

## Adrenocorticosteroids

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The adrenal gland consists of the cortex & the medulla. Medulla secretes epinephrine, whereas cortex synthesizes & secretes two major classes of steroid hormones: adrenocorticosteroids (glucocorticoids & mineralocorticoids) & adrenal androgens.

Adrenal cortex is divided into three zones that synthesize various steroids from cholesterol & then secrete them as follows:

1. Outer zona (glomerulosa) produces mineralocorticoids (eg. aldosterone). Production of aldosterone is regulated primarily by the renin-angiotensin system.
  2. Middle zona (fasciculata) synthesizes glucocorticoids (eg. cortisol), which are involved with normal metabolism & resistance to stress.
  3. Inner zona (reticularis) secretes adrenal androgens (eg. dehydroepiandrosterone).
- Secretion of both glucocorticoids & adrenal androgens & to some extent mineralocorticoids is under the control of ACTH (corticotropin).
  - Glucocorticoids serve as feedback inhibitors of ACTH and CRH secretion.
  - Adrenal cortex hormones are used in replacement therapy, treatment & management of asthma as well as other inflammatory diseases, such as rheumatoid arthritis; treatment of severe allergic reactions and in the treatment of some cancers.

### Adrenocorticosteroids:

- Their receptors are intracytoplasmic.
- Glucocorticoid receptor is widely distributed throughout the body, whereas mineralocorticoid receptor is confined mainly to excretory organs (eg. kidney, colon, and salivary and sweat glands).
- Both glucocorticoid and mineralocorticoid receptors are found in the brain.
- Receptor-hormone complex is translocated into the nucleus, and acts as a transcription factor that turn genes on (if complexed with co-activators) or off (if complexed with co-repressors), depending on the tissue.

This mechanism requires time to produce an effect, but other glucocorticoid effects, such as their interaction with catecholamines to mediate bronchial relaxation or lipolysis are immediate.

### A. Glucocorticoids

Cortisol is the principal human glucocorticoid. Its production is diurnal, with a peak early in the morning (8:00 a.m.) followed by a decline and then a secondary, smaller peak in the late afternoon (1:00 a.m.). Stress and levels of the circulating steroid influence secretion. Glucocorticoids effects include:

#### **1. Promote normal intermediary metabolism:** by

- Favor gluconeogenesis through increasing amino acid uptake by the liver and kidney also they elevate the activities of gluconeogenic enzymes.
- Stimulate protein catabolism (except in the liver) and lipolysis, thereby providing the building blocks and energy that are needed for glucose synthesis (**note:** glucocorticoid insufficiency may result in hypoglycemia (eg. during stressful periods or fasting)).

- Glucocorticoid augmenting the action of GH on adipocytes, enhancing lipolysis.

## **2. Increase resistance to stress:**

- By raising plasma glucose levels, glucocorticoids provide the body with the energy it required to combat stress caused by, eg. trauma, fright, infection, bleeding, or debilitating disease.
- Glucocorticoids enhance the vasoconstrictor action of adrenergic stimuli on small vessels result in a modest rise in BP.

## **3. Alter blood cell levels in plasma:**

- Glucocorticoids redistribute eosinophils, basophils, monocytes and lymphocytes from the circulation to lymphoid tissue.
- Increase blood levels of Hb, erythrocytes, platelets and polymorphonuclear leukocytes.

**Note:** Although the decrease in circulating lymphocytes & macrophages compromises the body's ability to fight infections, but this is an important property in the treatment of leukemia.

## **4. Anti-inflammatory action:**

- The most important therapeutic property of glucocorticoids is the dramatic reduction of the inflammatory & immunologic responses. The exact mechanism is complex and incompletely understood, it is thought to be through:
  1. Lowering & inhibition of peripheral lymphocytes and macrophages.
  2. Inhibition of phospholipase A2 (due to elevation of lipocortin), blocking the release of arachidonic acid from membrane-bound phospholipid.
  3. Reduction of Cox-2 synthesis, lowering the availability of prostaglandins.
  4. Interference with mast cell degranulation, decreasing histamine & capillary permeability.

## **5. Effects on endocrine system:**

Elevated level of glucocorticoids cause feedback inhibition of corticotropin production, thus inhibiting further synthesis of both glucocorticoid and TSH.

## **6. Effects on other systems:**

- Adequate cortisol levels are essential for normal glomerular filtration.
- Effects of corticosteroids on other systems are mostly associated with the adverse effects of the hormones.
- High doses of glucocorticoids stimulate gastric acid & pepsin production and may exacerbate ulcers.
- On CNS, the influence on mental status has been identified.
- Chronic glucocorticoid therapy can cause severe bone loss & myopathy.

## **B. Mineralocorticoids:**

- They control water volume and concentration of electrolytes, especially sodium & potassium.
- Aldosterone causes reabsorption of sodium, bicarbonate and water. While it decreases reabsorption of potassium. Aldosterone also enhances sodium reabsorption in GI mucosa, sweat & salivary glands.

**Note:** Elevated aldosterone levels may cause alkalosis & hypokalemia, whereas sodium and water retention lead to an increase in blood volume and BP.

- Hyperaldosteronism is treated with **spironolactone** (aldosterone antagonist).

**Therapeutic uses of the adrenal corticosteroids:**

Several semisynthetic derivatives of the glucocorticoids have been developed, they vary in their anti-inflammatory potency, mineralocorticoid activity & duration of action as follows:

| Duration of action                | Glucocorticoids           | Anti-inflammatory effect | Salt-retaining effect |
|-----------------------------------|---------------------------|--------------------------|-----------------------|
| Short acting (1-12 hours)         | Hydrocortisone            | 1                        | 1                     |
|                                   | Cortisone                 | 0.8                      | 0.8                   |
| Intermediate acting (12-36 hours) | Prednisone                | 4                        | 0.8                   |
|                                   | prednisolone              | 5                        | 0.8                   |
|                                   | Methylprednisolone        | 5                        | 0.5                   |
|                                   | Triamcinolone             | 5                        | 0                     |
| Long acting (36-55 hours)         | Betamethasone             | 35                       | 0                     |
|                                   | Dexamethasone             | 30                       | 0                     |
|                                   | <b>Mineralocorticoids</b> |                          |                       |
|                                   | Fludrocortisone           | 10                       | 125                   |
|                                   | Desoxycorticosterone      | 0                        | 20                    |

The therapeutic uses of adrenal corticosteroids include:

**1. Replacement therapy:**

**a. Primary adrenocortical insufficiency (Addison disease):**

Caused by adrenal cortex dysfunction. **Hydrocortisone** (identical to natural cortisol), is given to correct the deficiency. 2/3 of **hydrocortisone** daily dose is given in the morning and 1/3 is given in the afternoon (to mimic the daily circadian rhythm). **Fludrocortisone**, (potent synthetic mineralocorticoid with some glucocorticoid activity), may also be given to raise the mineralocorticoid activity to normal levels.

**b. Secondary or tertiary adrenocortical insufficiency:**

Caused by a defect in the production of CRH or ACTH. **Hydrocortisone** is used for treatment of these deficiencies (**note:** synthesis of mineralocorticoids in the adrenal cortex is less impaired than that of glucocorticoids).

**c. Congenital adrenal hyperplasia (CAH):**

Group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones. This condition may lead to virilization in females due to overproduction of adrenal androgens.

- The choice of replacement hormone depends on the specific enzyme defect. The administration of corticosteroids suppresses the release of CRH and ACTH, thus it decreases production of adrenal androgens.

## 2. Diagnosis of Cushing syndrome:

Cushing syndrome is caused by a hypersecretion of glucocorticoids due to excessive release of corticotropin by the anterior pituitary or an adrenal tumor.

- **Dexamethasone** suppression test is used to diagnose & differentiate the cause of Cushing syndrome. **Dexamethasone** suppresses cortisol release due to pituitary- dependent Cushing syndrome, but not suppress glucocorticoid released from adrenal tumors.

**Note:** Iatrogenic Cushing syndrome is caused by chronic treatment with high doses of glucocorticoid.

## 3. Relief of inflammatory symptoms & immunosuppression:

Glucocorticoids dramatically reduce the manifestations of inflammation (eg. rheumatoid and osteoarthritic inflammation as well as skin inflammatory conditions). The effect of glucocorticoids on the inflammatory process is the result of a number of actions, including:

- a. Redistribution of leukocytes to other body compartment.
- b. Increase the concentration of neutrophils.
- c. Decrease the concentration of lymphocytes (T & B cells), basophils, eosinophils & monocytes.
- d. Inhibit the responses of leukocytes & macrophages to mitogens & Ags.
- e. The glucocorticoids central anti-inflammatory action is the inhibition of PGs & LTs production.
- f. They also reduce histamine release from basophils & mast cells, thus diminishing the activation of the kinin system.

## 4. Treatment of allergies:

Symptoms of bronchial asthma, allergic rhinitis & drug, serum & transfusion allergic reactions can be treated with glucocorticoids. Inhalation of beclomethasone, triamcinolones & others can minimize systemic effects.

## 5. Acceleration of lung maturation:

Fetal cortisol regulates lung maturation. A dose of beclomethasone is given I.M to the mother 48 hours prior to birth, followed by a 2<sup>nd</sup> dose 24 hours before delivery can be used to prevent the development of respiratory distress syndrome in premature infants.

## Pharmacokinetics:

- All glucocorticoids can be administered orally (readily absorbed from GIT).
- Selected agents can also be given I.V, I.M, intra-articularly (into arthritic joints), topically or as aerosol (for inhalation).

- Hepatic dysfunction may dramatically increase glucocorticoids half- lives.
- During pregnancy **prednisone** is preferred, it is a prodrug that is not converted to the active compound **prednisolone** in the fetal liver. Also any **prednisolone** formed in the mother is biotransformed to **prednisone** by the placental enzymes.

**Note:** **Cortisone, desoxycorticosterone, triamcinolone** can be given I.M, while **dexamethasone, hydrocortisone, methylprednisolone & prednisone** can be given I.M or I.V. **Beclomethasone, flunisolide, fluticasone & triamcinolone** can be given as inhaler. Also **beclomethasone, dexamethasone, hydrocortisone & triamcinolone** can be used topically.

- Dose selection is affected by many factors, including glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation & time of day of the drug administration. Large doses of the hormone administered for more than 2 weeks cause suppression of the hypothalamic- pituitary- adrenal (HPA) axis. The alternate-day administration is a useful regimen that can allows the HPA axis to recover/ function on the days at which the hormone is not taken.

#### **Adverse effects:**

Long- term corticosteroid therapy can cause:

1. Osteoporosis (most common) because glucocorticoids inhibit intestinal absorption of  $Ca^{2+}$ , inhibit bone formation & decrease sex hormone synthesis (patient is advised to take calcium & vitamin D supplements).
2. Increased appetite, but it is one of the reasons for the use of **prednisone** in cancer chemotherapy.
3. Cushing – like syndrome (centripetal redistribution of body fat, puffy face, hirsutism, acne, HT, insomnia & increased appetite can occurs when excess corticosteroids are present.
4. Decreased growth in children, impaired wound healing & increased risk of infection.
5. Emotional disturbances (euphoria, depression).
6. Hypertension & peripheral edema.
7. Peptic ulcer.
8. Glaucoma & cataract may occur with long- term corticosteroid therapy.
9. Hyperglycemia that may develop to D.M. (diabetic should monitor their blood glucose & adjust their medication accordingly).
10. Hypokalemia (can be counteracted by potassium supplementation).

**Note:** Coadministration of hepatic inducer or inhibitor drugs may require dose adjustment of glucocorticoids

#### **Withdrawal**

In patient who experienced HPA suppression, abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal. This risk, coupled with the possibility of psychological dependence on the drug and the fact that withdrawal might cause an exacerbation of the disease, means the dose must be

tapered according to the individual, possibly through trial and error. The patient must be monitored carefully.

## **Inhibitors of adrenocorticoid biosynthesis or function**

Several substances have proven to be useful as inhibitors to the synthesis or function of adrenal steroids:

### **1. Metyrapone:**

- Interferes with the final step of glucocorticoid synthesis, leading to an increase in 11-deoxycortisol & adrenal androgens & the potent mineralocorticoid 11-deoxycorticosterone.
- Used for adrenal function tests & treatment of pregnant women with Cushing's syndrome
- Can cause salt & water retention, hirsutism, dizziness & GI disturbances.

### **2. Aminoglutethimide:**

- Inhibits the conversion of cholesterol to pregnenolone, reducing the synthesis of all corticosteroids.
- Used in treatment of breast cancer (it has largely replaced by tamoxifen), it is used in conjunction with dexamethasone. Also it is used in treatment of adrenal cortex malignancies.

### **3. Ketoconazole:**

- Antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. Used for the treatment Cushing's syndrome.

### **4. Trilostane:**

- Inhibits aldosterone, cortisol & gonadal hormone synthesis. Causes GI side effects.

### **3. Mifepristone:**

- At high doses it is a potent glucocorticoid antagonist as well as antiprogesterin.
- Its use is limited for the treatment of inoperable patient with ectopic ACTH syndrome.

### **6. Spironolactone:**

- Antihypertensive drug competes on mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney.
- It can also antagonize aldosterone & testosterone synthesis.
- Effective against hyperaldosteronism.
- Useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle. Adverse effects are hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

### **7. Eplerenone:**

- An aldosterone antagonist, gynecomastia that is associated with the use of **spironolactone** is not occurred with the use of **eplerenone**. Approved as an antihypertensive.