

## Summary

**Glucorticoids** (cortisol and Corticosterone) are a class of steroid hormones that are produced in the **zona fasciculata** of the adrenal cortex.

**Glucorticoids** exert their effects by binding either to: **A. Cytosolic receptor** or **B. Membranous (present on the cellular membrane) or both.**

**A) Cytosolic receptor binding alters DNA transcription of the steroids' response element (genomic effect) to induce (e.g. lipocortin) or repress (e.g. certain cytokines and chemokines) the synthesis of proteins. This effects take hours to days.**

**B) Membranous receptor binding** (at cell membrane) uses second messenger systems to cause rapid effects in mins to hours.

**Glucorticoids** have different effects on different body processes that enable the body to cope with stress, and summarized as follows:

1. **Metabolic effects:** on carbohydrates (increases gluconeogenesis and **and glucose resistance by cells**), **proteins** (increases extrahepatic protein metabolism, growth retardation, and osteoporosis), and **fats metabolism** (increases lipolysis and fat redistribution) in a way that favors **high blood glucose levels**.
2. **Inhibition of immune and inflammatory responses:** reducing the release of immune and inflammatory mediators; reduce the activity of inflammatory cells, and reduction of edema.
3. **Anti-vitamin D effect:** Increase urinary excretion and decrease the intestinal absorption of  $\text{Ca}^{2+}$
4. **HPA Suppression:** suppress **CRH and ACTH** secretion, which occurs with **high doses**, but may lead to **adrenal insufficiency with sudden withdrawal**.
5. **Other effects:** Euphoria or psychotic states. This effects may occur due to CNS electrolyte changes and **enhancement of vascular responsiveness to catecholamine to maintain blood pressure**

## Pharmacokinetics:

### Absorption:

Effective **orally**, while parenteral and other preparation forms are also available.

Can get absorbed systemically when given at local sites (e.g. skin, respiratory tract, etc.) but in very are mild concentrations that may cause some slight adverse systemic effects. This risk is reduced with fluorinated preparations.

**Distribution:** 90% or more of cortisol in plasma is transported by reversible binding to Corticosteroids Binding Globulin (CBG) & to albumin. Only the unbound free form is active & can enter cells by diffusion

**Metabolism:** are metabolized by the liver, where some preparations transform to active form in liver like:

Cortisone → Hydrocortisone

Prednisone → Prednisolone

**t<sub>1/2</sub>:** is variable [ short, intermediate & long acting ]

**Excretion:** as soluble sulphates in the urine.

- The only preparation used in emergency situations is cortisol
- the two preparations that are used in the inhaler form are **fluticasone** and **budesonide (because the undergo very slight first metabolism)**.
- Because the face and the genital area are sensitive areas, a mild or moderate preparation in the form of a **cream** should be used, and that to avoid certain conditions and adverse effects.
- Time of administration of GCs, especially on prolonged use, should follow natural circadian rhythm i.e. person should take it **in the early morning**. Alternating days of administration is also **useful in reducing suppression of HPA**.
- Indications:

A-Hormone Replacement Therapy

**1- Adrenal Insufficiency: Adrenal Crisis (Emergency situation)**

## 2 - Addison's Disease

### 3- Cushing Syndrome: In Diagnoses ➔ Dexamethasone suppression test while In Treatment ➔ Cortisol

B-Immunosuppressive Therapy: 1- **Severe allergic reactions** 2-**Diseases of allergic origin** 3-**Autoimmune disorders** 4-**Organ transplantation** 5-**Blood dyscrasias** 6- **Acute gout**

C- Other indications:

1. **Raised intracranial pressure** 6-**In neoplastic diseases**: 7-**As antiemetic regimens**: to prevent and cure emesis of chemotherapy 8-**Suppress excess ACTH production**
- **Adverse effects of corticosteroids depend on dosage and duration** of therapy and can be related to one of the three effects:
  - 1) **Inhibition** of the **hypothalamic-Pituitary-Adrenal Axis** (if more than 2 weeks)
  - 2) **Iatrogenic Cushing Syndrome** (slowly withdraw GCs if possible, if not treatment concurrent symptoms. See graph for Cushing's adverse effects)
  - 3) **Other effects**: **Hyperglycemia**, **muscle wasting**, **fat redistribution**, **menstrual irregularities**, **avascular necrosis of head of femur**

**Contraindications**: Diabetes mellitus, Hypertension or heart failure, History of mental disorders or

Epilepsy, Osteoporosis, Peptic ulcer, Presence of infection or Tuberculosis ➔ requires chemotherapy before administration

**Preactions**:

- Patients receiving GCs for adrenal insufficiency and are subjected to major stress (e.g. surgery) should have their doses doubled
- In children receiving ➔ take care of live attenuated vaccines.
- In pregnant women; better avoid fluorinated GCs ➔ teratogenicity
- Newborns to mothers taking high dose GCs ➔ -ve HPA axis

## Review questions

### 1. Which of the following is a pharmacologic effect of exogenous glucocorticoids?

- (A) Increased muscle mass
- (B) Hypoglycemia
- (C) Inhibition of Leukotriene synthesis.
- (D) Improved wound healing
- (E) Increased excretion of salt and water.

### 2. A 34-yr-old woman with ulcerative colitis has required long-term treatment with pharmacologic doses of a glucocorticoid agonist. Which of the following is a toxic effect associated with long-term glucocorticoid treatment?

- (A) A "lupus-like" syndrome.
- (B) Adrenal gland neoplasm
- (C) Hepatotoxicity
- (D) Osteoporosis
- (E) Precocious puberty in children.

### 3. A 46-yr-old male patient has Cushing's syndrome that is due to the presence of an adrenal tumor. Which of the following drugs would be expected to reduce the signs and symptoms of this man's disease?

- (A) Betamethasone
- (B) Cortisol
- (C) Fludrocortisone
- (D) Ketoconazole
- (E) Triamcinolone

**4. Which of the following best describes a glucocorticoid response element?**

- (A) A protein regulator that controls the interaction between an activated steroid receptor and DNA
- (B) A short DNA sequence that binds tightly to RNA polymerase
- (C) A small protein that binds to an unoccupied steroid receptor protein and prevents it from becoming denatured
- (D) A specific nucleotide sequence that is recognized by a Steroid hormone receptor-hormone complex
- (E) The portion of the steroid receptor that binds to DNA

**5. Glucocorticoids have proved useful in the treatment of which of the following medical conditions?**

- (A) Chemotherapy-induced vomiting
- (B) Essential hypertension
- (C) Hyperprolactinemia
- (D) Parkinson's disease
- (E) Type II diabetes

**6.) A 56-yr-old woman with systemic lupus erythematosus had been maintained on a moderate daily dose of prednisone for 9 mo. Her disease has finally gone into remission and she now wishes to gradually taper and then discontinue the prednisone. Gradual tapering of a glucocorticoid is required for recovery of which of the following?**

- (A) Depressed release of insulin from pancreatic B cells
- (B) Hematopoiesis in the bone marrow.
- (C) Normal osteoblast function.
- (D) The control by vasopressin of water excretion.
- (E) The hypothalamic-pituitary-adrenal system.

**7.) A 54-yr-old man with advanced tuberculosis has developed signs of severe acute adrenal insufficiency. Which of the following signs or symptoms is this patient most likely to exhibit?**

- (A) A moon face
- (B) Dehydration
- (C) Hyperglycemia
- (D) Hypertension.
- (E) Hyperthermia

- **Answer Key: 1:C - 2:D – 3:D – 4:D – 5:A – 6:E – 7:B**

**CORTICOSTEROIDS**

C-Cushing's syndrome  
O-osteoporosis  
R-retardation of growth  
T-thin skin n easy bruisability  
I-infections in immunosuppression  
C-cataract and glaucoma  
O-odema  
S-suppression of HPA axis  
T-thinning and ulceration of gastric mucosa  
E-Emotional disturbance  
R-rise in BP and Na<sup>+</sup> retention  
I-Increase in hair growth (hirsutism)  
O- others like hypokalemia  
D- Delayed wound healing  
S-stria

**A mnemonic of the effects of corticosteroids**