Adrenal Corticosteroids

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The Adrenal Gland Consists of 2 Parts:

1. Medulla which secrete epinephrine
2. Cortex which produces corticosteroids and androgens

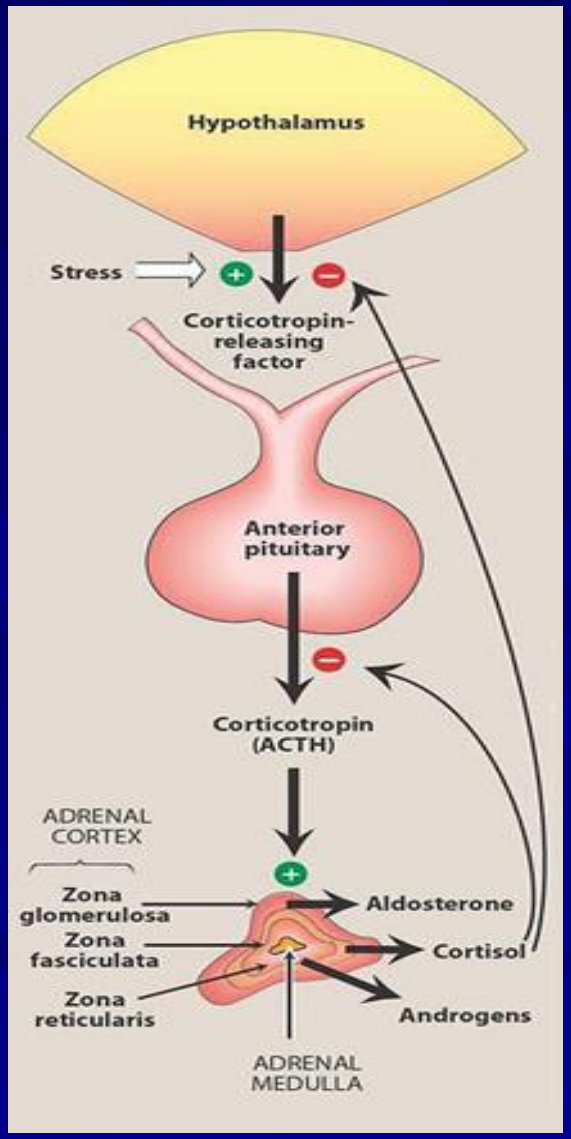
Adrenal Corticosteroids

- Mineralocorticoids from Zona Glomerulosa: Aldosterone
- Glucocorticoids from Zona fasciculata : Cortisol

Corticosteroid Divided Into:

1. Glucocorticoids (Cortisol)
2. Mineralocorticoids (Aldosterone)
   - Regulation of corticosteroid secretion in response to adrenocorticotropic Hormone from the anterior pituitary (ACTH) and this hormone secreted under control of the hypothalamic corticotropin-releasing hormone (CRH).

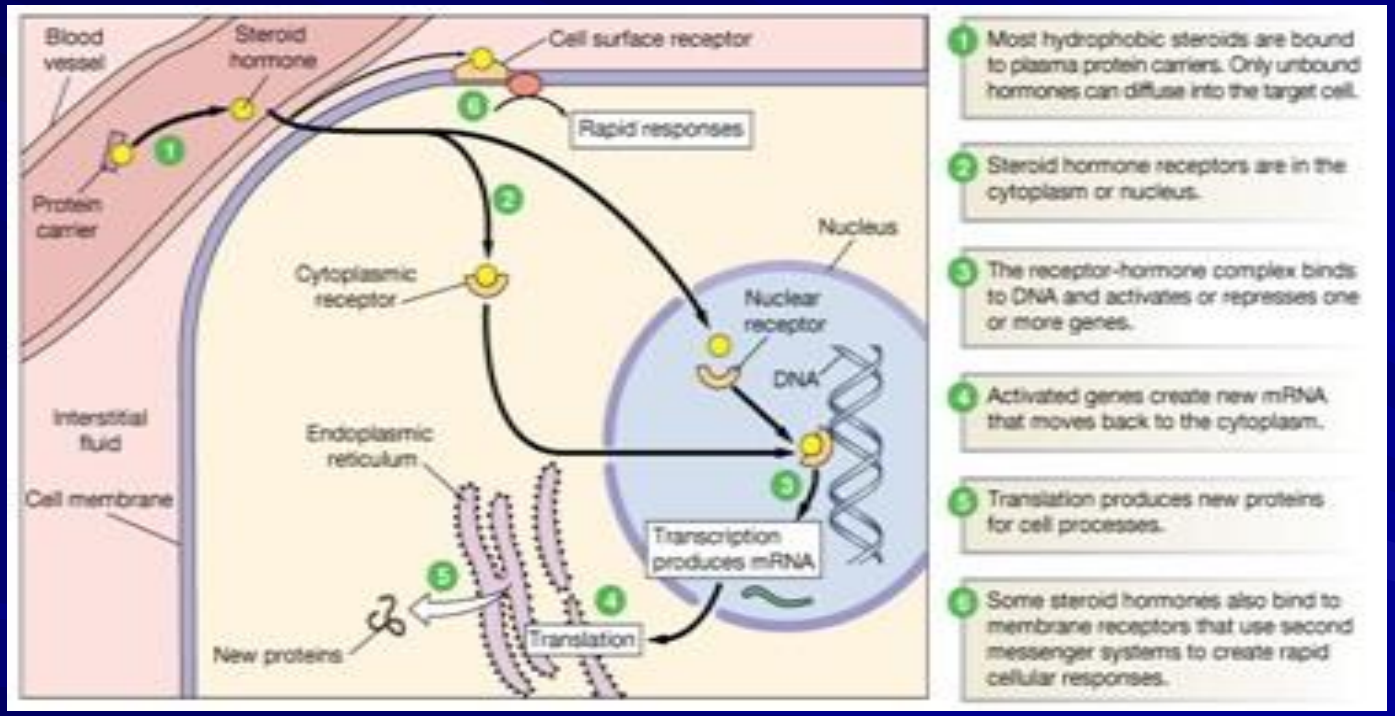
Adrenocortical Hormones

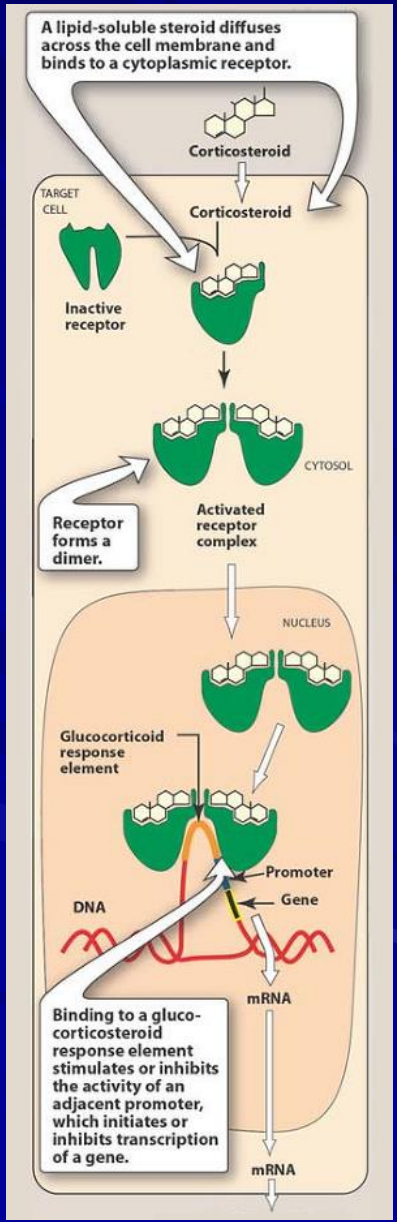


Mechanism of Action

- Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
- They bind to specific intracellular receptors in target tissues.
- The receptor-hormone complex binds to DNA and activates or represses one or more genes.
- Activated genes create new mRNA that move back to cytoplasm.
- Translation produces new proteins for cell processes

Mechanism of Action





Physiological Effects

Mineralocorticoids: aldosterone

- Mineralocorticoids (aldosterone action) help to control the body's water volume and concentration of electrolytes, especially sodium and potassium (enhancement reabsorption of sodium, bicarbonate and water and increase urinary execration of potassium), this leads to an increase in blood volume and blood pressure.

Physiological Effects
Glucocorticoids:

1. Regulate carbohydrate metabolism: gluconeogenesis is increased and peripheral glucose utilization decreased
2. Regulate protein metabolism: anabolism is decreased, stimulate catabolism and provides amino acid for glucose synthesis
3. Regulate fat deposition and promote lipolysis (fat breakdown)

Other Physiological Effects

4. Anti-inflammatory and immunosuppressant, Interrupt the inflammatory processes by:
   - Inhibit synthesis of chemical mediators (histamine, prostaglandin and leukotriense).
   - Promoting specific regulatory proteins
5. Increase resistance to stress by raising plasma glucose levels
6. Glucocorticoids can cause a modest rise in blood pressure, by the vasoconstrictor action of adrenergic stimuli on small vessels.

Other Physiological Effects

6. Affect mood, CNS excitability
   Glucocorticoid insufficiency is associated with depression, lethargy.
7. Suppression of HPA adrenocortical feedback system
8. Alter blood cell levels in plasma
   - ↓ Eosinophils, basophils, monocytes and lymphocytes
   - ↑ The blood levels of hemoglobin, erythrocytes, platelets and polymorphonuclear leukocytes.

Hydrocortisone (cortisol)

- Short acting
- Orally, i.v. ,intra - articular
- Hydrocortisone Sodium Succinate Inj. for quick (1-2 h) effect
- For continuous effect about 8-hourly administration is appropriate.

Corticosteroids

- Prednisolone
- Fluorinated corticosteroids (triamcinolone)
- Dexamethasone
- Betamethasone

Prednisolone

- Orally or i.m.
- Intermediate acting
- Has anti-inflammatory
- For anti-inflammatory pharmacotherapy
- With little sodium-retaining activity

Fluorinated Corticosteroids:

Triamcinolone

Has no sodium retaining mineralocorticoid.

May cause muscle wasting, anorexia and mental depression

Dexamethasone, Betamethasone:

- (long acting) and have powerful anti-inflammatory steroids.
- They are used for therapeutic adrenocortical suppression.

Therapeutic Uses of the Adrenal Corticosteroids On Adrenal Disorder

- Adrenal crisis
- Addison's disease
- Congenital adrenal hyperplasia
- Diagnosis of Cushing's syndrome
- On lung maturation in the fetus

1. Replacement therapy of acute adrenocortical insufficiency (adrenal crisis) which is duo to:
   - Failure to provide patient receiving replacement therapy with adequate doses
   - Abrupt withdrawal from chronic ,high dose glucocorticoid

Therapy consists of:

- Correction of fluid and electrolyte abnormalities by i.v. fluid and salts
- Hydrocortisone sodium succinate or phosphate in doses of 100 mg i.v. every 8 hours until the patient is stable. The dose is then gradually reduced, achieving maintenance dosage within 5 days.

2. Replacement therapy of chronic adrenocortical insufficiency (Addison's disease)
   - Primary adrenal insufficiency, about 15-25 mg orally in two to three divided dose of hydrocortisone must be given daily, contain (glucocorticoid activity and some minerelocorticoid)
   - Secondary (decrease secretion of ACTH by pituitary) and tertiary (decrease secretion of CRH by hypothalamus) adrenocortical insufficiency the treatment similar to that in primary.

3. Congenital adrenal hyperplasia excess adrenal androgen secretion is suppressed by prednisolone or dexamethasone which inhibit pituitary corticotropin production

4. Diagnosis of Cushing's syndrome: hypersecretion of glucocorticoids that results either from excessive release of corticotropin by the anterior pituitary or an adrenal tumor. The dexamethasone suppression test is used, dexamethasone suppresses cortisol release in individuals with pituitary dependent Cushing's syndrome, but it does not suppress glucocorticoid release from adrenal tumors

5. On 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 (RDS) in infants delivered prematurely.
   - Betamethasone is chosen because maternal protein binding and placental metabolism of this corticosteroid is less than that of cortisol, allowing increased transfer across the placenta to the fetus.

Therapeutic Uses of the Adrenal Corticosteroids On Non adrenal Disorders :

- Systemic inflammation
- Infections
- Inflammatory conditions of bones and joints
- Organ transplants
- Renal disorder
- Skin disease
- Hematological disorder
- Pulmonary disease
- Allergic reactions
- Eye disease
- Gastrointestinal disease

Adverse Effects

1. Endocrine
   - Iatrogenic Cushing's syndrome result in moon face, deposition of fat on the body, oedema, hypertension, striae, acne and hirsutism
   - Hypothalamic / pituitary / adrenal (HPA) suppression

2. Musculoskeletal: myopathy, Osteoporosis fractures of vertebrae, ribs
3. Immune: Suppression of the inflammatory response to infection and immunosuppression
4. Gastrointestinal: Peptic ulcer and hemorrhage
5. Central nervous system. Depression and psychosis Euphoria, insomnia, aggravation of schizophrenia and epilepsy
6. Ophthalmic effects cataracts and glaucoma (related to age, dosage)
7. Hypertention, Odema, Hypokalemia
8. Growth retardation due to reduce DNA synthesis and decreased cell division

Adverse Effects

Withdrawal Of Pharmacotherapy

Withdrawal from these drugs can be a serious problem, because if the patient has experienced HPA suppression, abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal and withdrawal might cause an exacerbation of the disease, means the dose must be tapered according to duration of therapy, the longer the duration of therapy the slower must be the withdrawal.

Adrenal Corticosteroids and Pregnancy

- Teratogenic in animals (fluorinated steroids are more teratogenic)
- Cleft palate and other fetal abnormalities may occur
- Dosage during pregnancy should be low

Drug Interactions

1. Increase hypokalemia when used with digoxin or thiazide diuretic.
2. Increase risk of peptic ulcer when used with anti inflammatory drug.
3. Decrease antibody responses to vaccines.
4. Antagonist the action of insulin and hypoglycemic agent

Inhibitors of Corticosteroid Synthesis

Aminoglutethimide

- Inhibiting the conversion of cholesterol to pregnenolone (stop synthesis of all steroids)
- It is used in breast cancer and malignancies of the adrenal cortex

Inhibitors of Corticosteroid Synthesis

Ketoconazole

- Inhibits all gonadal and Adrenal steroid hormone synthesis.
- It is used for Cushing's syndrome

Glucocorticoid Antagonist
Mifepristone

- It is a potent glucocorticoid antagonist.
- It forms a complex with the glucocorticoid receptor, but the rapid dissociation of the drug from the receptor leads to a faulty translocation into the nucleus.

Aldosterone Antagonist Spironolactone

- This antihypertensive drug competes for the mineralocorticoid receptor and thus, inhibits sodium reabsorption in the kidney
- It can also antagonize aldosterone and testosterone synthesis.
- Effective against Hyperaldosteronism.