Corticosteroids

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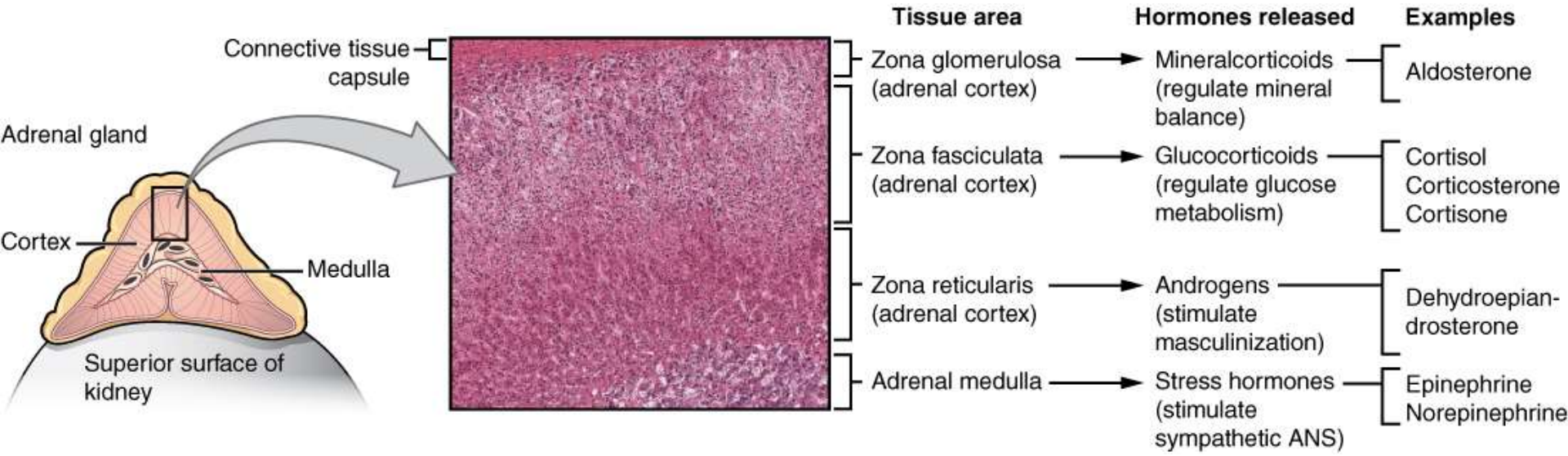
Adrenal hormones

- **Adrenal gland consists of:**
  - **Medulla:** secretes **epinephrine**
  - **Cortex:** synthesizes & secretes two classes of **steroids hormones:**
  - **Adrenocorticosteroids: (glucocorticoids, mineralocorticoids)**
  - **Androgens**

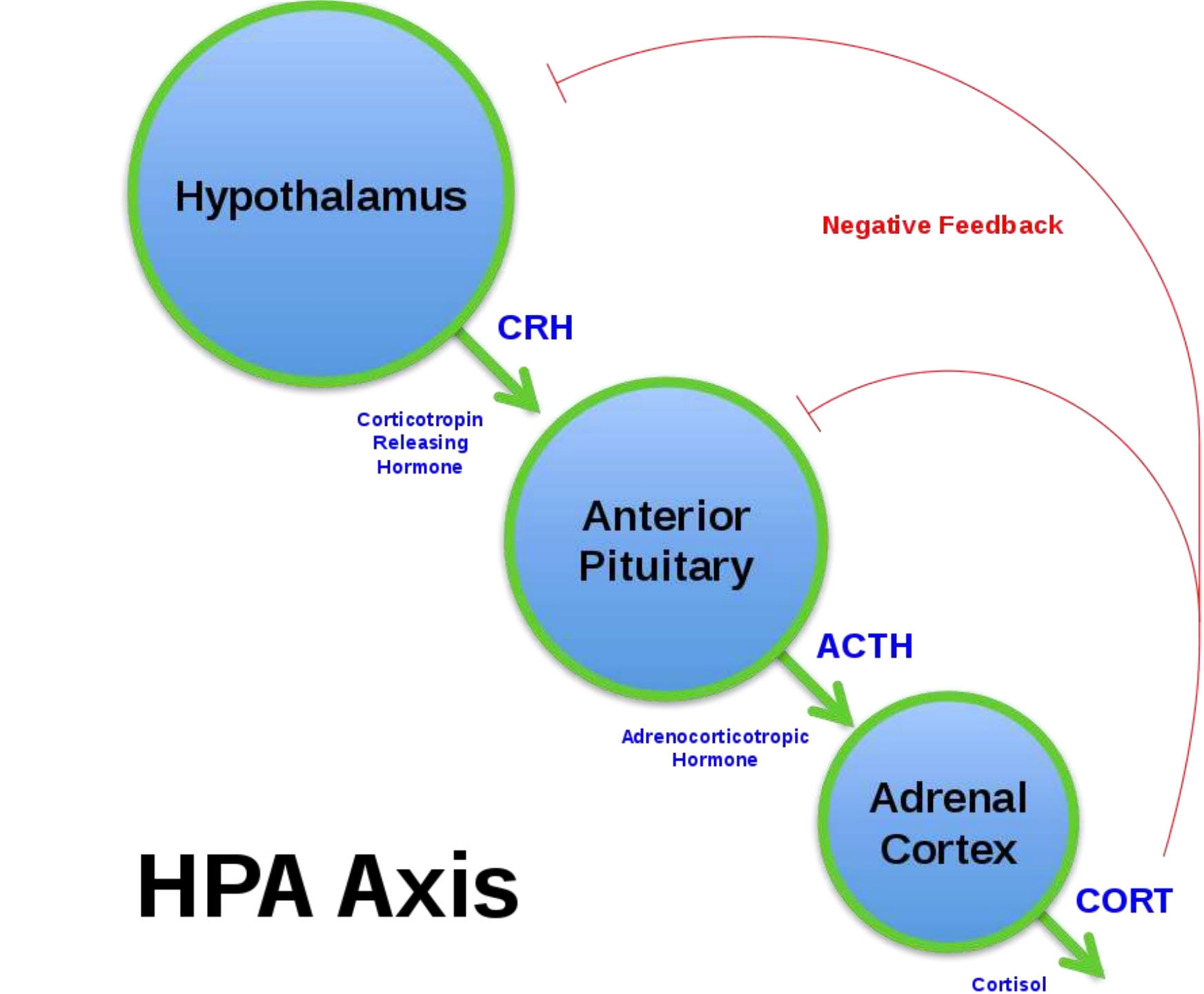
Adrenal Cortex

- **Adrenal cortex** is divided into **three zones** that synthesizes various steroids from cholesterol:
- **Outer zona: glomerulosa** produces mineralcorticosteroids (aldosterone)
- **Middle zone: fasciculata** synthesizes glucocorticoids (cortisol)
- **Inner zona: reticularis** secrets adrenal androgens


Connective tissue capsule
Adrenal gland
Cortex
Medulla
Superior surface of kidney
Tissue area
Hormones released
Examples
Zona glomerulosa (adrenal cortex)
Mineralcorticoids (regulate mineral balance)
Aldosterone
Zona fasciculata (adrenal cortex)
Glucocorticoids (regulate glucose metabolism)
Cortisol
Corticosterone
Cortisone
Zona reticularis (adrenal cortex)
Androgens (stimulate masculinization)
Dehydroepian-drosterone
Adrenal medulla
Stress hormones (stimulate sympathetic ANS)
Epinephrine
Norepinephrine

Regulation of Gulococorticoids secretion

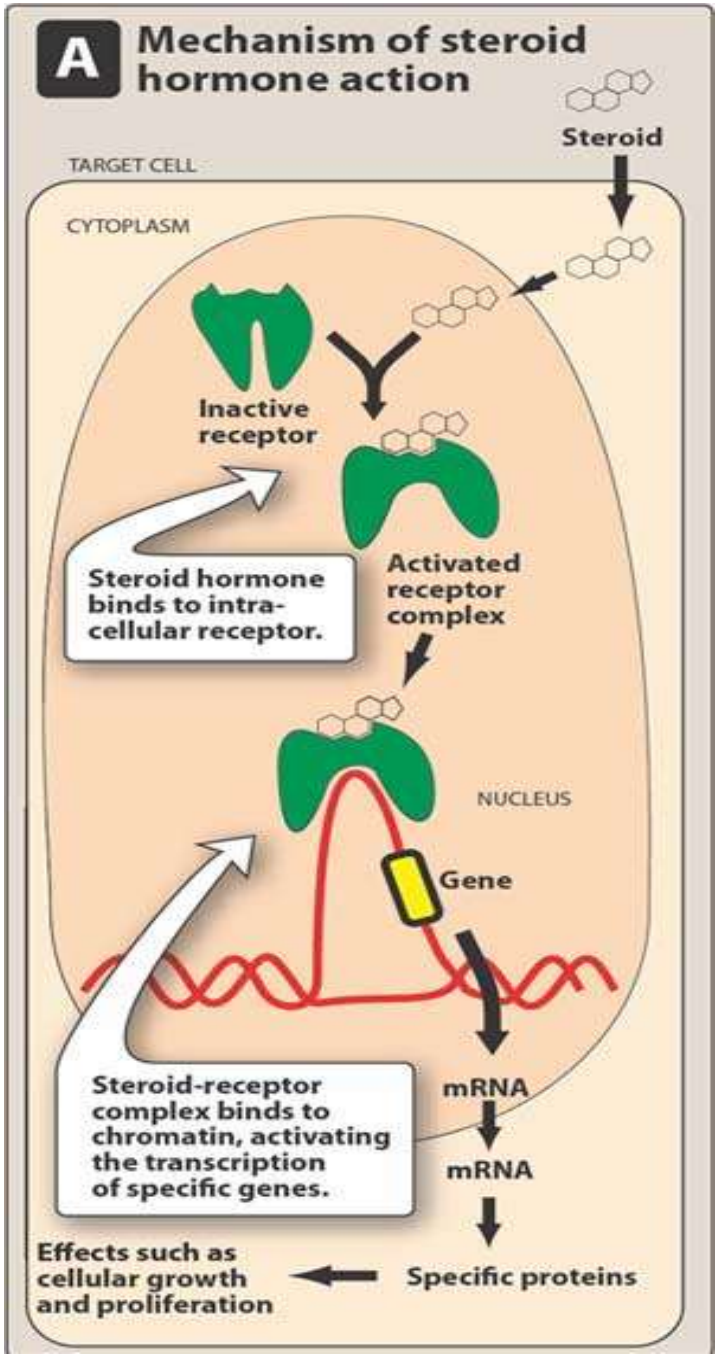
- Secretion by is controlled by pituitary corticotropin (**A**dreno**C**orticotropic **H**ormone **(ACTH)**
- ACTH is released in response to hypothalamus Corticotropin-Releasing Hormone **(CRH)**
- Glucocorticoids serve as feedback inhibitors of ACTH & CRH


Hypothalamus
Negative Feedback
CRH
Corticotropin Releasing Hormone
Anterior Pituitary
ACTH
Adrenocorticotropic Hormone
Adrenal Cortex
CORT
Cortisol

HPA Axis

Adrenocorticosteroids

- Adrenocorticosteroids bind to specific intracellular cytoplasmic receptors
- **Glucocorticostreroids** receptor is widely distributed
- **Mineralcorticosteroids** receptor is confined to excretory organs such as kidney, colon, salivary glands & sweat glands


A
Mechanism of steroid hormone action
Steroid
TARGET CELL
CYTOPLASM
Inactive receptor
Steroid hormone binds to intra-cellular receptor.
Activated receptor complex
NUCLEUS
Gene
Steroid-receptor complex binds to chromatin, activating the transcription of specific genes.
mRNA
mRNA
Specific proteins
Effects such as cellular growth and proliferation

Glucocorticoids

- Principal human glucocorticoid is **Hydrocortisone (cortisol)**
- Its production is **diurnal**, **with peak early in the morning** followed by decline, and then **secondary smaller peak** in late **afternoon**
- Factors that affect steroid secretion are **stress** & **level of circulation steroid**

Effects of cotrisol

- Carbohydrate metabolism:

- Promotes gluconeogenesis; hyperglycemia

- Protein metabolism:

- Decrease conversion of amino acid to protein; osteoporosis, slow growth children, skin atrophies, delay wound healing

- Fat deposition: increased on face, shoulders, & abdomen

Effects of cotrisol

- Increase blood pressure
- Blood cells:
  - Increase Hg, erythrocytes, platelets, neutrophils
  - Decrease eosinophils, basophils, monocytes, lymphocytes (compromises ability to fight infections)

Effects of cotrisol

- **Anti-inflammatory action:**
- Reduce inflammatory response, suppress immunity
- Lower peripheral lymohocytes & macrophages
- Indirection inhibition of phospholipase A2, arachidonic acid, the precursor of prostaglandins & leukotrienes
- Interfere in mast cell degranulation results in **decease histamine & capillary permeability**

Effects of cotrisol:

- High doses of glucocorticoids stimulate gastric acid & pepsin production & may exacerbate peptic ulcers
- Chronic therapy can cause severe bone loss
- Myopathy, weakness

Therapeutic use of adrenal corticosteroids

- They vary in their:
- Anti-inflammatory potency
- Degree to which they cause sodium retention
- Duration of action

Types of Glucocorticoids

- **Short acting (1-12 hrs)**
  - Hydrocotisone, cortisone
- **Intermediate acting (12-36 hrs)**
  - Prednisone, prednisolone, methylprednisolone, triamcinolone
- **Long acting (36-55 hrs)**
  - Betamethasone, dexamethasone

Types of glucocorticoids

- **Fluorinated corticosteroids: triamcinolone, fludrocortisone**

- **Triamcinolone:**
  - no sodium-retaining effect
  - Disadvantages:
  - muscle wasting, anorexia & mental depression

Types of glucocorticoids

- **Beclomethasone, budesonide, fluticasone** are suitable for use by **inhalation** for **asthma, intra-nasally for hay fever**

Therapeutic use of adrenal corticosteroids

- Addison's disease (primary adrenocortical insufficiency):
  - Is caused by adrenal cortex dysfunction
  - Treated with hydrocortisone
- Secondary or tertiary adrenocortical insufficiency:
  - Is caused by defect either in production of CRH by hypothalamus or ACTH by pituitary
  - Treated with hydrocortisone

Therapeutic use of adrenal corticosteroids

- **Relief inflammatory symptoms:** such as rheumatoid arthritis, autoimmune diseases
- By Lower blood concentration of leukocytes, lymphocytes, basophils, eosinophils, monocytes
  - Decrease production of prostaglandins & leukotrienes
  - Reduce histamine release by basophils & mast cells

Therapeutic use of adrenal corticosteroids

- **Treatment of allergies:**
  - Bronchial asthma, allergic rhinitis
- Beclomethasone, triamcinolone are applied topically by inhalation

Pharmacokinetics

- **Route of administration:**
- **All corticosteroids can be given orally**
- **IM:** cortisone, triamcinolone
- **IV, IM:** dexamethazone, hyrdocortisone, methyprednisolone, prednisolone
- **Aerosol:** beclomethasone, fluticasone, triamcinolone

Pharmacokinetics

- **Topically: (skin, lung, joints)**
- Beclomethasone, dexamethasone, hyrocortisone
- **Intra-articularly:** hydrocortisone

Dosage

- When **large doses** are required over extended period of time **(more than 2 weeks)**, suppression **of Hypthalamus-Pituitary Axis (HPA)** occurs
- **Alternate-day administration** is useful, it allows HPA to recover

Adverse effects

- Osteoporosis (most common)
- Cushing-like syndrome: redistribution of body fat, moon face, increase hair growth, acne, insomnia, increased appetite
- Cataract and glaucoma
- Hyperglycemia, diabetes mellitus
- Hypokalemia
- Tendon rupture

Adverse effects

- Impaired wound healing
- Emotional disturbances: psychosis, euphoria, depression
- Hypertension
- Peptic ulcer
- Decreased growth in children
- Hirsutism

Withdrawal

- Abrupt withdrawal from these drugs can be a **serious** problem
- Abrupt withdrawal inhibits CRH hypothamic production and results in adrenal failure
- If patient has experienced hypothalamus-pituitary-axis suppression (HPA), this may cause acute adrenal insufficiency syndrome, that can be **fatal**

- Therefore, corticosteroids must be withdrawn **gradually** to allow hypothalamus, pituitary and adrenal regain normal function

Adrenal steroid during pregnancy

- Are teratogenic in animals
- Dosing during pregnancy should be kept low
- Fluorinated steroids should be avoided because they more teratogenic
- The only glucocorticoid that has no effect on fetus during pregnancy is **prednisone**

Contraindications

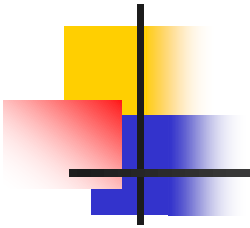
- Patients with history of diabetes
- History of mental disorder
- Peptic ulcer
- Hypertension
- Heart failure
- Epilepsy
- Tuberculosis

Mineralocorticosteroids

- Control body's water volume, electrolytes especially sodium & potassium
- **Aldosterone** acts on kidney tubules, collecting ducts, GI mucosa, sweat & salivary glands

Mineralcorticosteroids

- **Aldosterone** causes reabsorption of sodium and water, increases the excretion of potassium
- Hyperaldosteronism is treated with spironolactone



- Cortisone, hydrocortisone, fludrocortisone, have significant mineralcorticoid activity
- Prednisolone, betamethasone & dexamethasone: have little mineralcorticoid activity (sodium-retaining activity)