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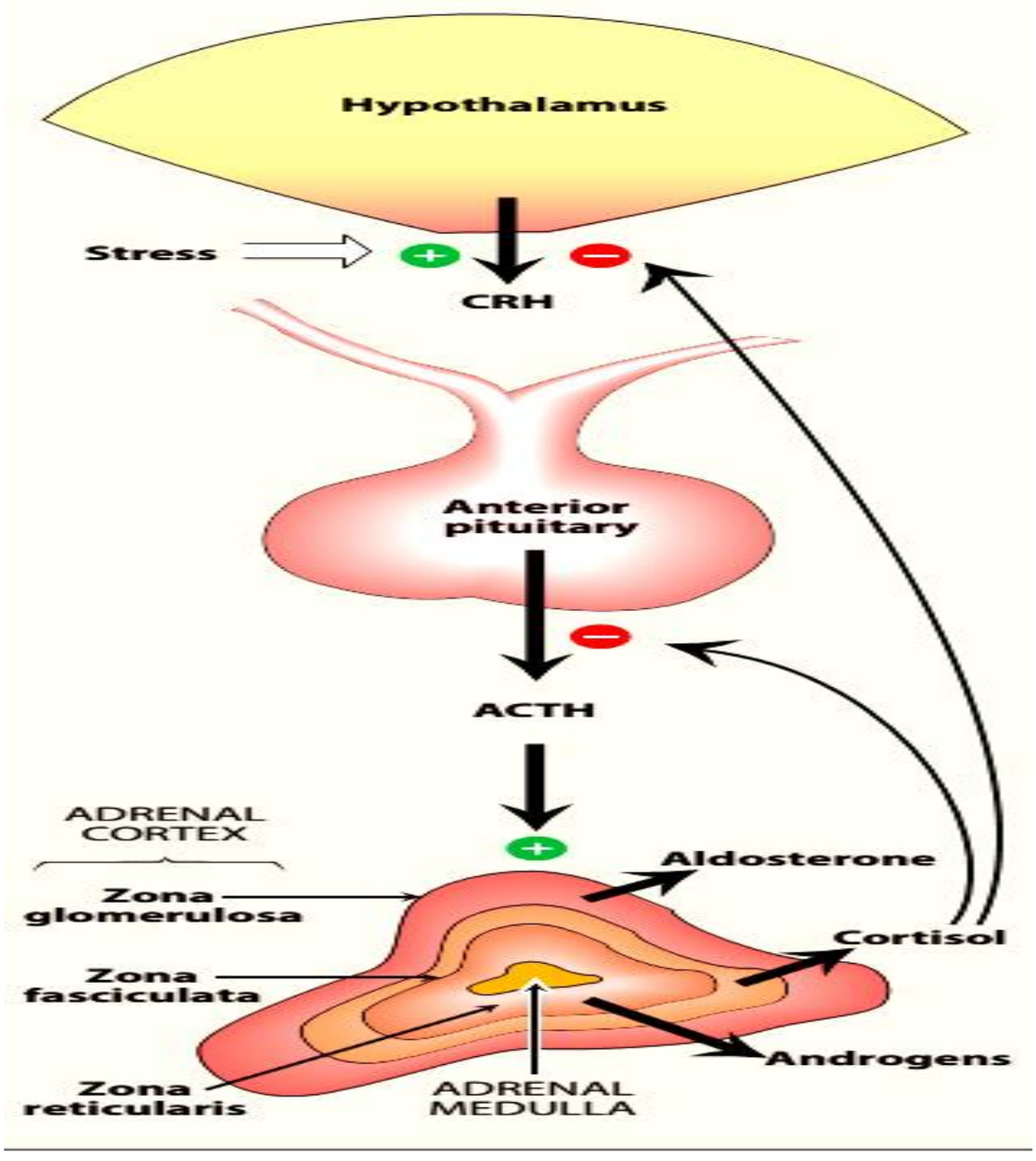
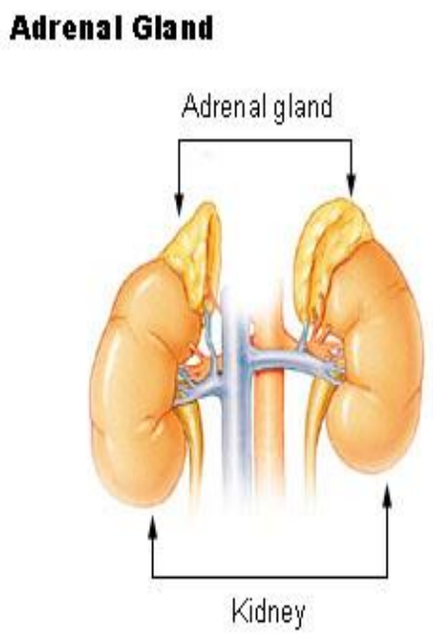
Adrenocorticosteroids & Adrenocortical Antagonists





Adrenal gland

The adrenal cortex synthesize two types of steroids:

1- corticosteroids which include:

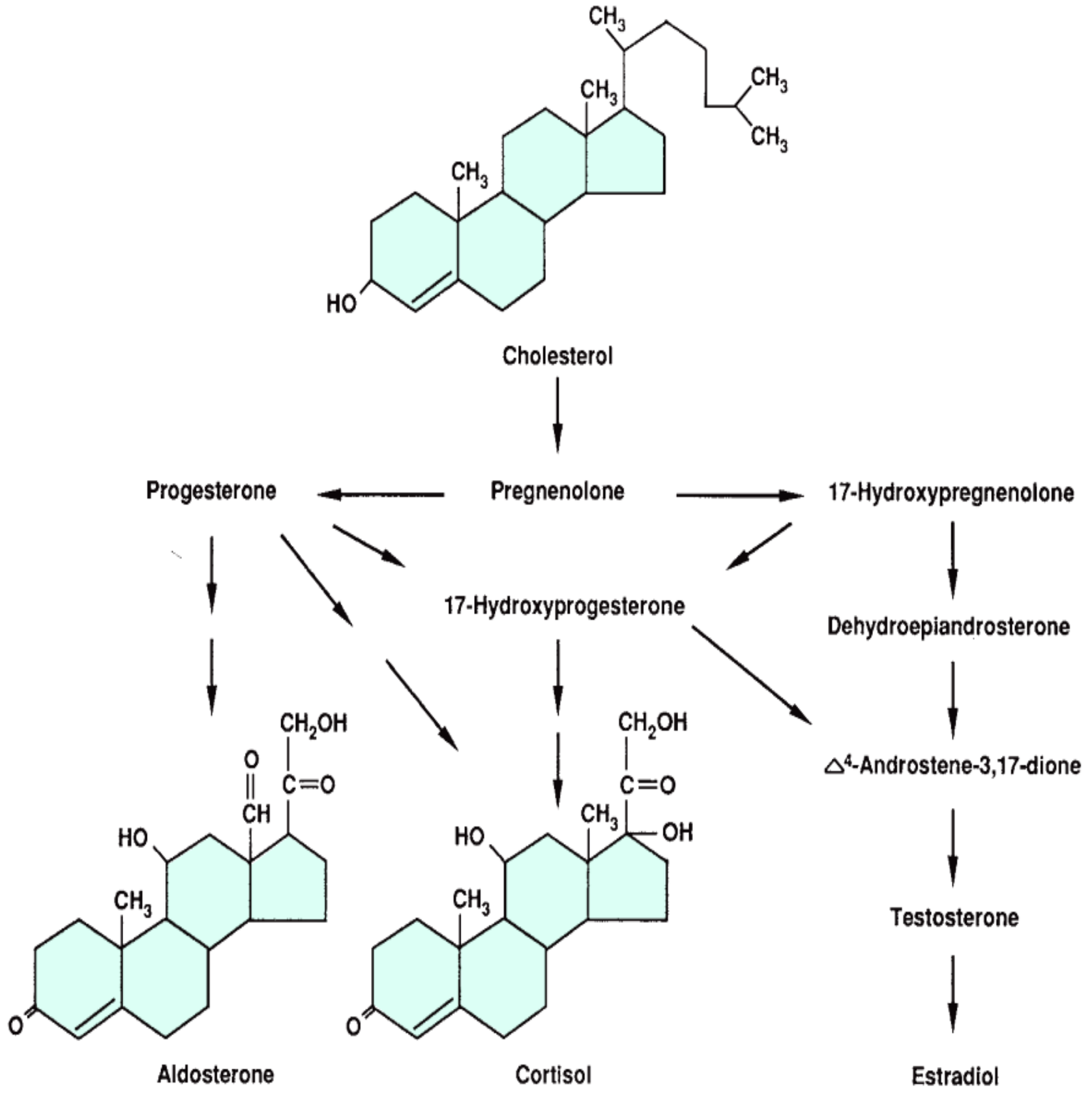
a- Glucocorticoids, include: **Hydrocortisone** (cortisol), **cortisone**, **corticosterone**.

b- Minerlaocorticoids, include **aldosterone**, **Deoxycorticosterone**

2- Adrenal androgens: include **dehydroepiandrosterone** (DHEA), **androsterone**, **testosterone**.

Stimuli	Part	Principal product
Angiotensin II	Zona glomerulosa	Aldosterone
ACTH	Zona fasiculata & reticularis	Cortisol Adrenal androgens
Sympathetic nervous system	Medulla	Adrenaline & Nor-adrenaline

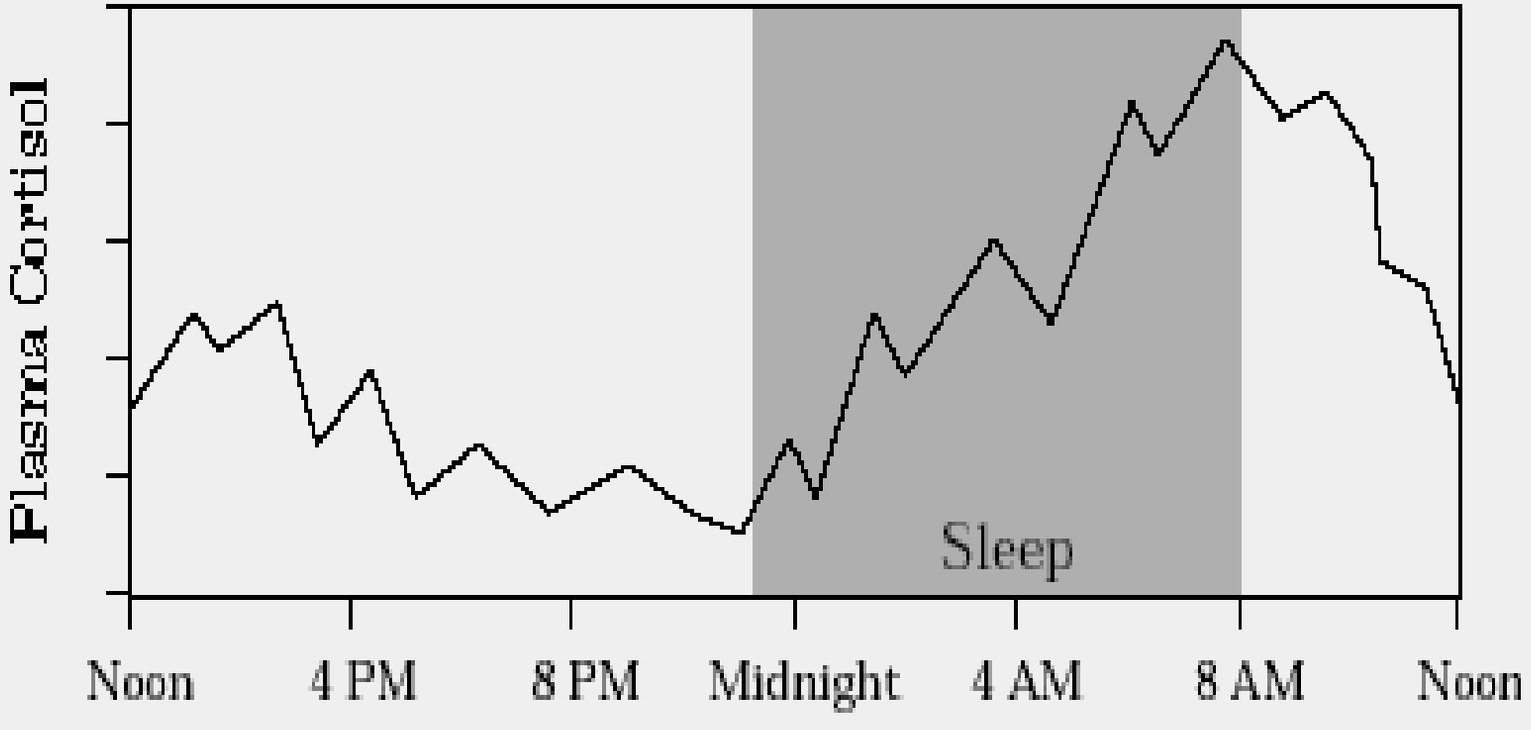
Basal secretions		
Group	**Hormone**	**Daily secretions**
Glucocorticoids	• Cortisol • Corticosterone	5 – 30 mg 2 – 5 mg
Mineralocorticoids	• Aldosterone • deoxycorticosterone	5 – 150 mg Trace
Sex Hormones Androgen •Progesten •Oestrogen	 DHEA (dehydroepiandrosterone) • Progesterone • Oestradiol	 15 – 30 mg 0.4 – 0.8 mg Trace


Cholesterol
Progesterone
Pregnenolone
17-Hydroxypregnenolone
17-Hydroxyprogesterone
Dehydroepiandrosterone
△4-Androstene-3,17-dione
Testosterone
Estradiol
Aldosterone
Cortisol

I- Glucocorticoids

They are secreted under the influence of **ACTH** from the pituitary gland.
The major glucocorticoids in humans is **cortisol** (hydrocortisone).
$T_{1/2}$ of cortisol is 90-110 minutes.

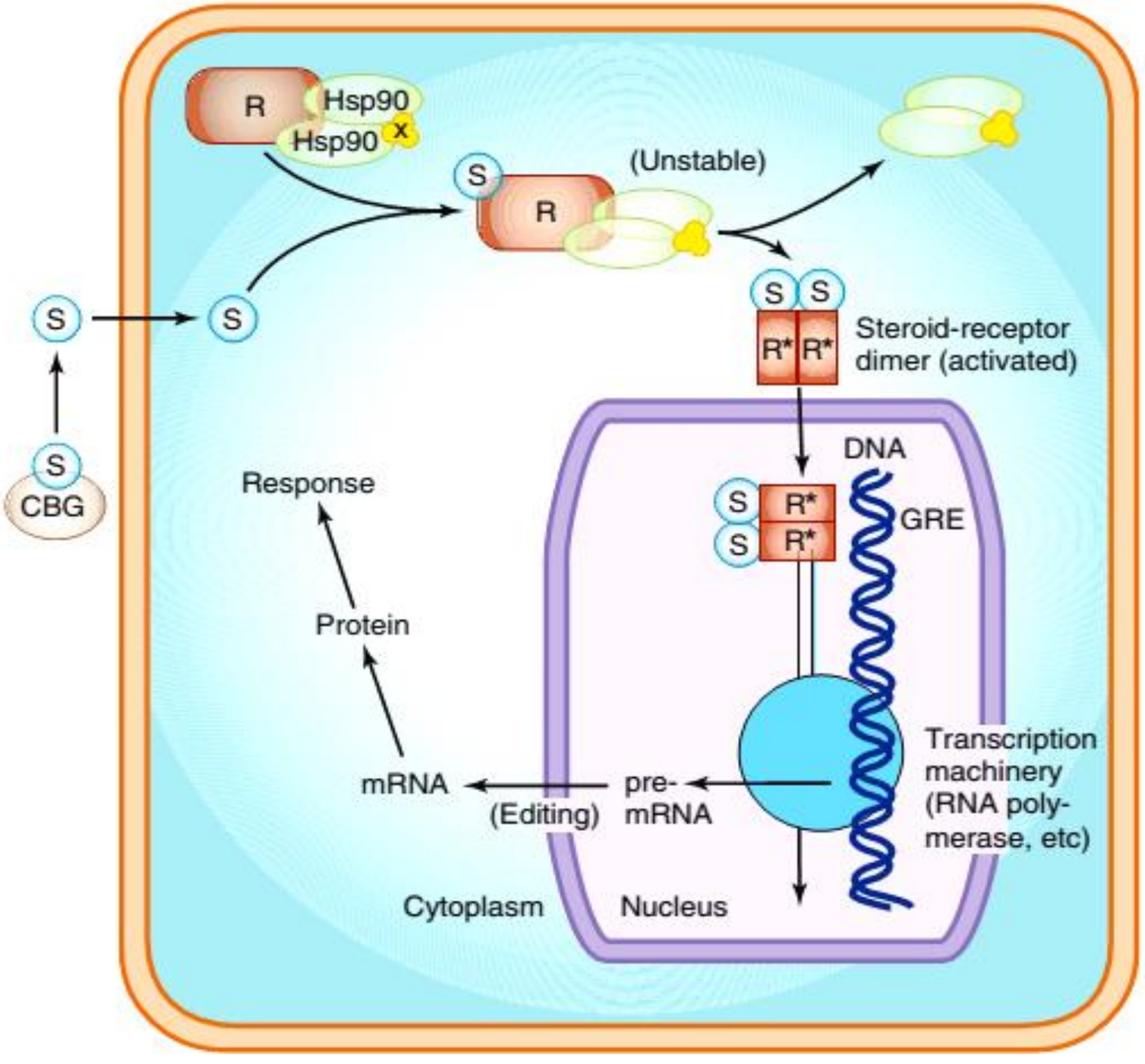
Circadian rhythm



Mechanism of Action:

The effects of mineralocorticoids and glucocorticoids are mediated by two separate and specific intracellular receptors, the **MR** (mineralocorticoid receptor) and **GR** (glucocorticoid receptor), respectively.

Natural and synthetic steroids enter cells rapidly and interact with these intracellular receptors. The resulting complexes modulate the transcription rate of specific genes and lead to an increase or decrease in the levels of specific proteins.


R
Hsp90
Hsp90
x
(Unstable)
S
R
S
S
S
S
R*
R*
Steroid-receptor
dimer (activated)
S
CBG
DNA
Response
S
R*
S
R*
GRE
Protein
Transcription
machinery
(RNA poly-
merase, etc)
mRNA
(Editing)
pre-
mRNA
Cytoplasm
Nucleus

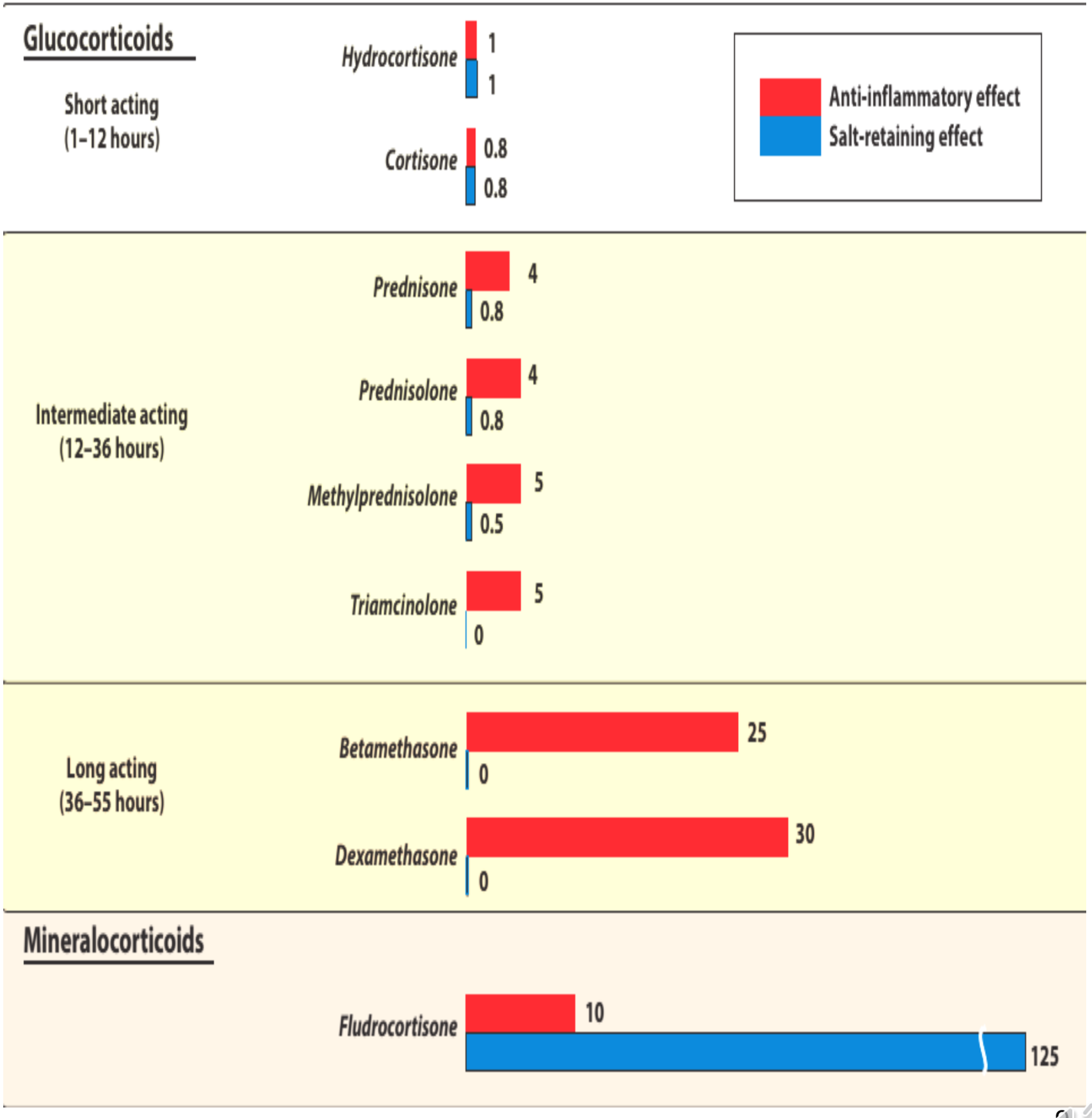
Mechanism of glucocorticoid action.

This figure models the interaction of a steroid (**S**; eg, **cortisol**), with its receptor (R) and the subsequent events in a target cell. The steroid is present in the blood bound to **corticosteroid-binding globulin (CBG)** but enters the cell as the free molecule. The intracellular receptor is bound to stabilizing proteins, including heat shock protein 90 (**Hsp90**) and several others (**X**).

When the complex binds a molecule of steroid, the Hsp90 and associated molecules are released. The steroid-receptor complex **enters the nucleus as a dimer**, binds to the **glucocorticoid response element (GRE**) on the gene, and regulates gene transcription. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response.

Preparations

Drug	Anti-inflammatory effect (relative potency to cortisol)	doses
A- Glucocorticoids		
1- short acting (8-12h):		
Cortisol	1	20 mg
Cortisone	0.8	25 mg
2- Intermediate acting (12-36h):		
Triamcinolone	5	4 mg
Paramethasone	10	2 mg
Prednisone	4	5 mg
Prednisolone	5	5 mg
Methylprednisolone	5	4 mg
3- long acting (36-72h):		
Dexamethasone	30	0.75 mg
Flumethasone (0.3% cream)		0.3%
Betamethasone	25- 40	0.6 mg
B- Mineralocorticoids		
Fludrocortisone	10	2 mg
Deoxycorticosterone	0	


Glucocorticoids
Short acting
(1–12 hours)
Hydrocortisone
1
1
Cortisone
0.8
0.8
Anti-inflammatory effect
Salt-retaining effect
Intermediate acting
(12–36 hours)
Prednisone
4
0.8
Prednisolone
4
0.8
Methylprednisolone
5
0.5
Triamcinolone
5
0
Long acting
(36–55 hours)
Betamethasone
25
0
Dexamethasone
30
0
Mineralocorticoids
Fludrocortisone
10
125

Physiological and pharmacological actions of glucocorticoids:

Glucocorticoids affect virtually all tissues. Therapeutic actions and adverse effects are extensions of these physiologic effects.

(1) Physiologic effects

(a) The physiologic effects of glucocorticoids are mediated by increased protein breakdown, leading to a **negative nitrogen balance.**

(b) Glucocorticoids **increase blood glucose** levels by stimulation of **gluconeogenesis**.

(c) These agents increase the synthesis of several key enzymes involved in **glucose and amino acid metabolism**.

(d) Glucocorticoids **increase plasma fatty acids and ketone body** formation via **increased lipolysis** and decreased glucose uptake into fat cells and **redistribution of body fat.**

(e) These agents increase **kaliuresis** via increasing renal blood flow and glomerular filtration rate; increased protein metabolism results in release of intracellular potassium.

(f) Glucocorticoids decrease intestinal absorption of Ca^{2+} and inhibit osteoblasts.

(g) Glucocorticoids promote Na^{+} and water retention.

(2) Anti-inflammatory effects.

The anti-inflammatory effects of glucocorticoids are produced by the inhibition of all of the classic signs of inflammation (erythema, swelling, soreness, and heat). Specific effects include:

(a) Inhibition of the antigenic response of macrophages and leukocytes.

(b) Inhibition of **vascular permeability** by reduction of histamine release and the action of kinins.

(c) Inhibition of arachidonic acid and prostaglandin production by inhibition of phospholipase A2 (mediated by **annexin 1**) and the cyclooxygenases.

(d) Inhibition of cytokine production, including IL-1, IL-2, IL-3, IL-6, tumor necrosis factor-α

(3) Immunologic effects

(a) Glucocorticoids decrease circulating **lymphocytes, monocytes, eosinophils, and basophils.**

(b) Long-term therapy results in involution and atrophy of all lymphoid tissues.

(4) Other effects

(a) Inhibition of plasma ACTH and possible adrenal atrophy

(b) Inhibition of fibroblast growth and collagen synthesis

(c) Stimulation of acid and pepsin secretion in the stomach

(d) Altered CNS responses, influencing mood and sleep patterns

(e) Enhanced neuromuscular transmission

(f) Induction of **surfactant production in the fetal lung at term**

Pharmacological properties

► Both natural and synthetic steroids are **excreted by the kidney** following reduction and formation of glucuronides or sulfates.
►All of the steroids listed (except aldosterone) may be administered orally. A variety of glucocorticoids, including cortisol, prednisolone, and dexamethasone, can be injected IM or SC.
Various glucocorticoid preparations are available for rectal, or topical administration. Glucocorticoids administered as **inhalants** are used to treat **asthma**.
► **Agents with the longest half-life tend to be the most potent.**
(1) Short-acting agents such as cortisol are active for 8–12 h.
(2)Intermediate-acting agents such as prednisolone are active for 12-36h.
(3) Long-acting agents such as dexamethasone are active for 39–72 h.
► Drug administration attempts to pattern the **circadian rhythm**: A double dose is given in the morning, and a single dose is given in the afternoon.
► Alternate-day therapy relieves clinical manifestations of the disease state while causing **less severe suppression of the adrenal-hypothalamic-pituitary axis**. In this therapy, large doses of short-acting or intermediate-acting glucocorticoids are administered **every other day**.
►Patients removed from long-term glucocorticoid therapy must be **weaned off the drug over several days**, **using progressively lower doses to allow recovery of adrenal responsiveness.**

Therapeutic uses:

Replacement therapy in case of:

1- **Primary or chronic adrenal insufficiency** (**Addison`s disease**) whether due to atrophy or to partial destruction by tuberculosis, tumor or necrosis.

2- **Secondary adrenal insufficiency** due to lack of ACTH resulting from hypopituitratism

3- **Congenital adrenal hyperplasia** due to inborn errors in adrenal enzyme with resulting deficiency of cortisol and aldosterone synthesis.

Pharmacotherapy in non adrenal disorders

Glucocorticoids are widely used as anti-inflammatory, anti-allergic and immunosuppressive in variety of disease such as:

1- Allergic disease as hay fever, urticaria dermatitis and anaphylaxis.

2- Arthritis whether rheumatoid arthritis or gouty arthritis.

3- Bronchial asthma

4- Rheumatic carditis

5- Malignancy including leukemia, lymphoma and breast cancer.

6- Ocular diseases as conjunctivitis.

7- Cerebral edema. 8- ulcerative colitis

9- Septic shock 10- Some nephritic syndrome

11- Stimulation of surfactant production and acceleration of lung maturation in a preterm fetus.

Adverse Reactions:

-Adverse reactions of glucocorticoids may be due to either sudden withdrawal or result from continuous use of large doses.

- **Sudden withdrawal of glucocorticoids after prolonged therapy** produce symptoms of **adrenal insufficiency** due to suppression of endogenous secretion of the hormone. **This is characterized by anorexia, nausea, vomiting, fever, malaise, myalgia and arthralgia.**

- **Excessive doses and prolonged administration of glucocorticoids** produce varies manifestations:

a- Hyperglycemia and glucosuria b- Myopathy
c- Hypertension and aggravation of heart failure d- peptic ulceration
e- Muscle weakness, osteoprosis, reduced growth in children
f- Cushing`s syndrome (moon face, buffalo hump).

Contraindications:

1- Peptic ulcer 2- diabetes 3- glaucoma
4- psychosis 5- Infections
6- hypertension with congestive heart failure.