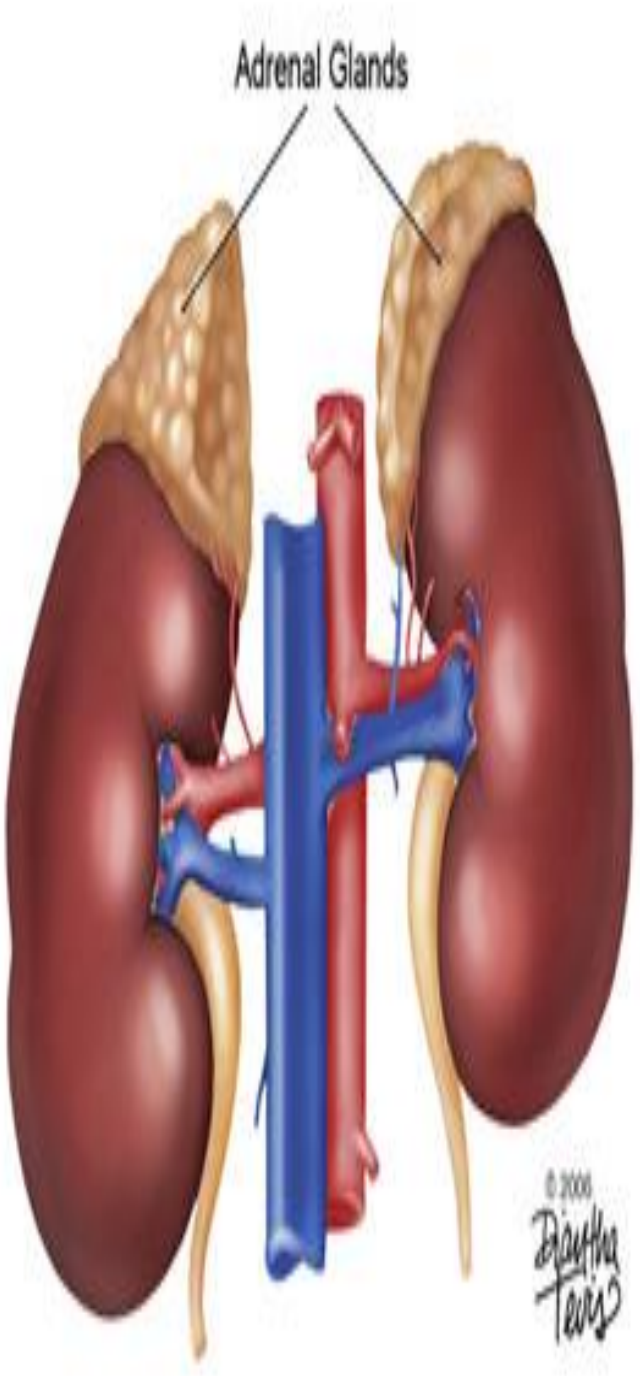


CORTICOSTEROIDS AGONISTS AND ANTAGONISTS

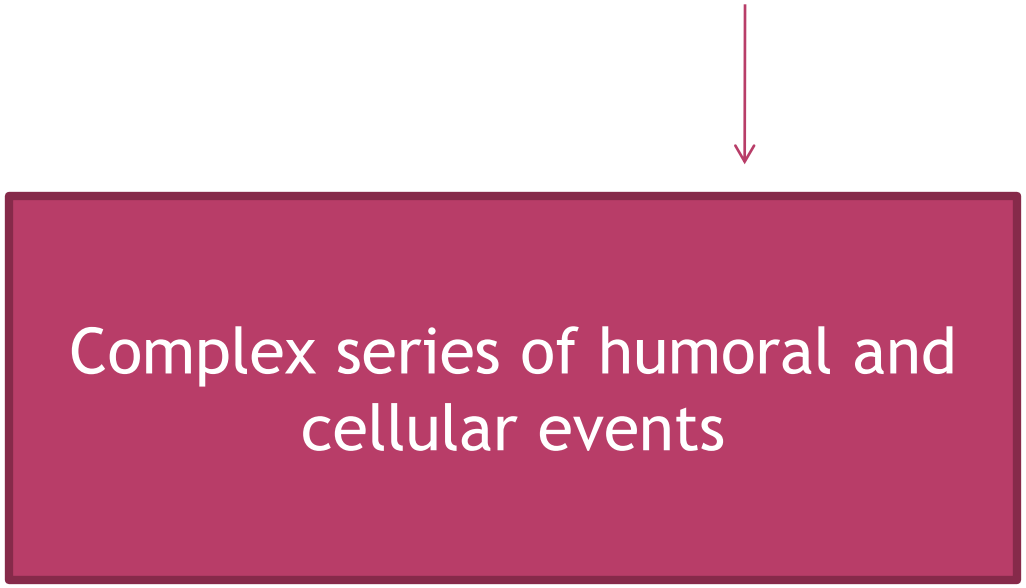
By : Azza Osman Yousif

MSc in clinical pharmacy

OBJECTIVES

- Identify the adrenal gland hormones
- Understand the classification of the steroids hormones.
- Discuss the synthesis and release of these hormones.
- Discuss their mechanism of action, pharmacokinetics, clinical uses and side effects.
- Identify their antagonists.

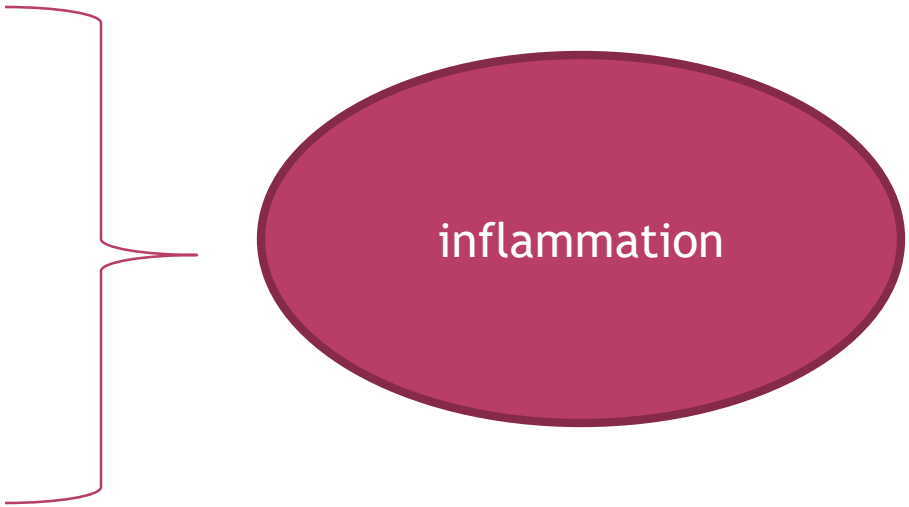
- Injurious stimuli → body



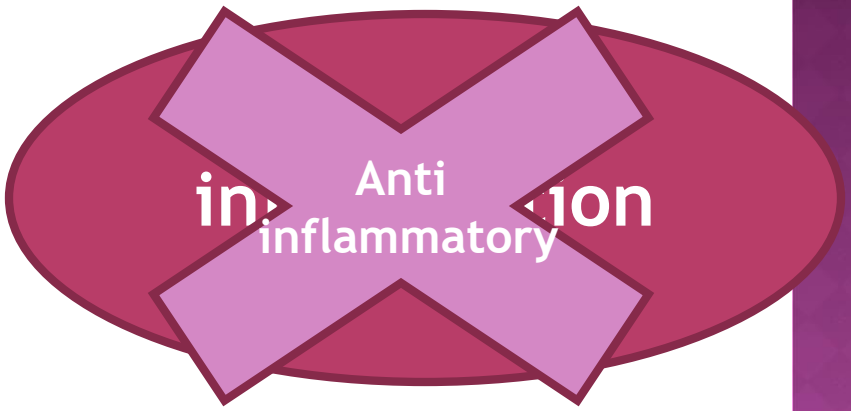
- Inflammation

- Swelling, Redness, Hotness ,Pain

- Inflammation is a multi-factorial process:
- Prostaglandins
- Histamine
- Leukotrienes
- Lymphocytes
- Macrophages
- …etc



- Inflammation is a multi-factorial process:
- Prostaglandins
- Histamine
- Leukotrienes
- Lymphocytes
- Macrophages
- …etc

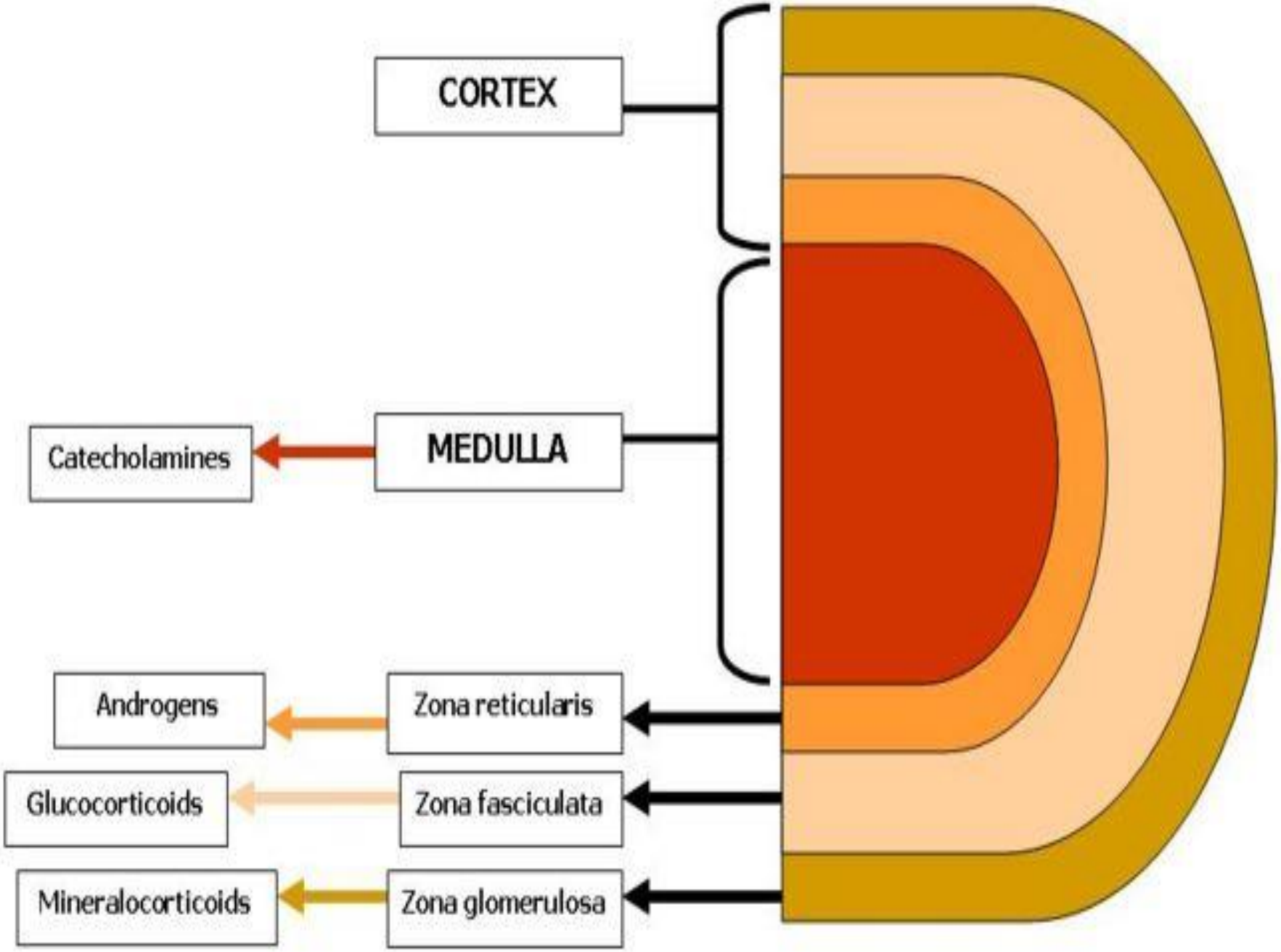


STEROIDS

- The adrenal glands consist of two parts:

- **The inner *medulla***, which secretes catecholamine.

- **The outer *cortex***, *which secretes* ***adrenal steroids.***


CORTEX
MEDULLA
Catecholamines
Androgens
Zona reticularis
Glucocorticoids
Zona fasciculata
Mineralocorticoids
Zona glomerulosa

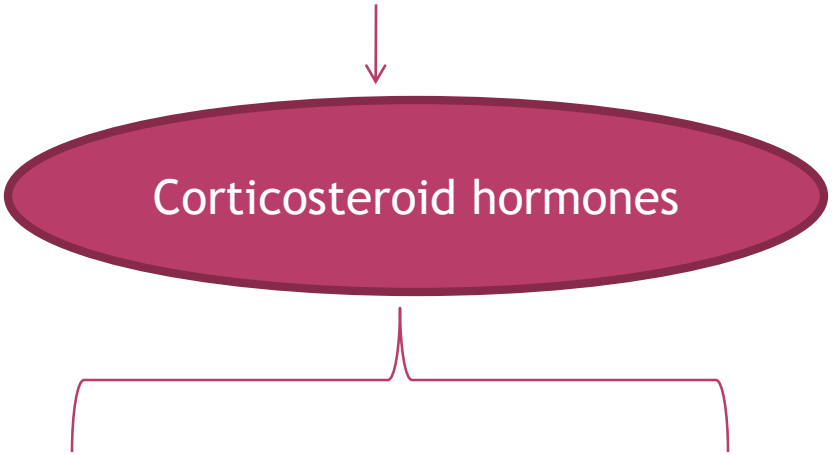
ADRENOCORTICAL STEROIDS

- The adrenal cortex synthesizes two classes of steroids: the *corticosteroids* **(glucocorticoids and mineralocorticoids).**

- The actions of corticosteroids historically were described as glucocorticoid (carbohydrate metabolism-regulating) and mineralocorticoid (electrolyte balance-regulating), reflecting their preferential activities.

- In humans, ***cortisol*** **(*hydrocortisone*)** is the main **glucocorticoid** and **aldosterone** is the main **mineralocorticoid**.

- Adrenal cortex



Mineralocorticoids:

- Which regulate
Sodium and potassium
reabsorption

Glucocorticoids:

-Metabolism, catabolism,
immune responses,
And anti-inflammation

- Glucocorticoids are most commonly employed for their anti-inflammatory and immunosuppressive properties. (metabolic effect>>> side effects).

The mineralocorticoid and glucocorticoid actions are not completely separated. **Naturally occurring steroids** and some glucocorticoids have quite substantial effects on **water and electrolyte balance**.

- In synthetic steroids:
- Gluco-corticoid effect could be partially separated from the mineralo-corticoid effect.

- But the anti inflammatory effect could not be separated from the other metabolic effects.

GLUCOCORTICOIDS SYNTHESIS AND RELEASE

- While they are always present, there is a well-defined **circadian rhythm** in the secretion in healthy humans.

- The net blood concentration being highest early in the morning, gradually diminishing throughout the day and reaching a low point in the evening or night.

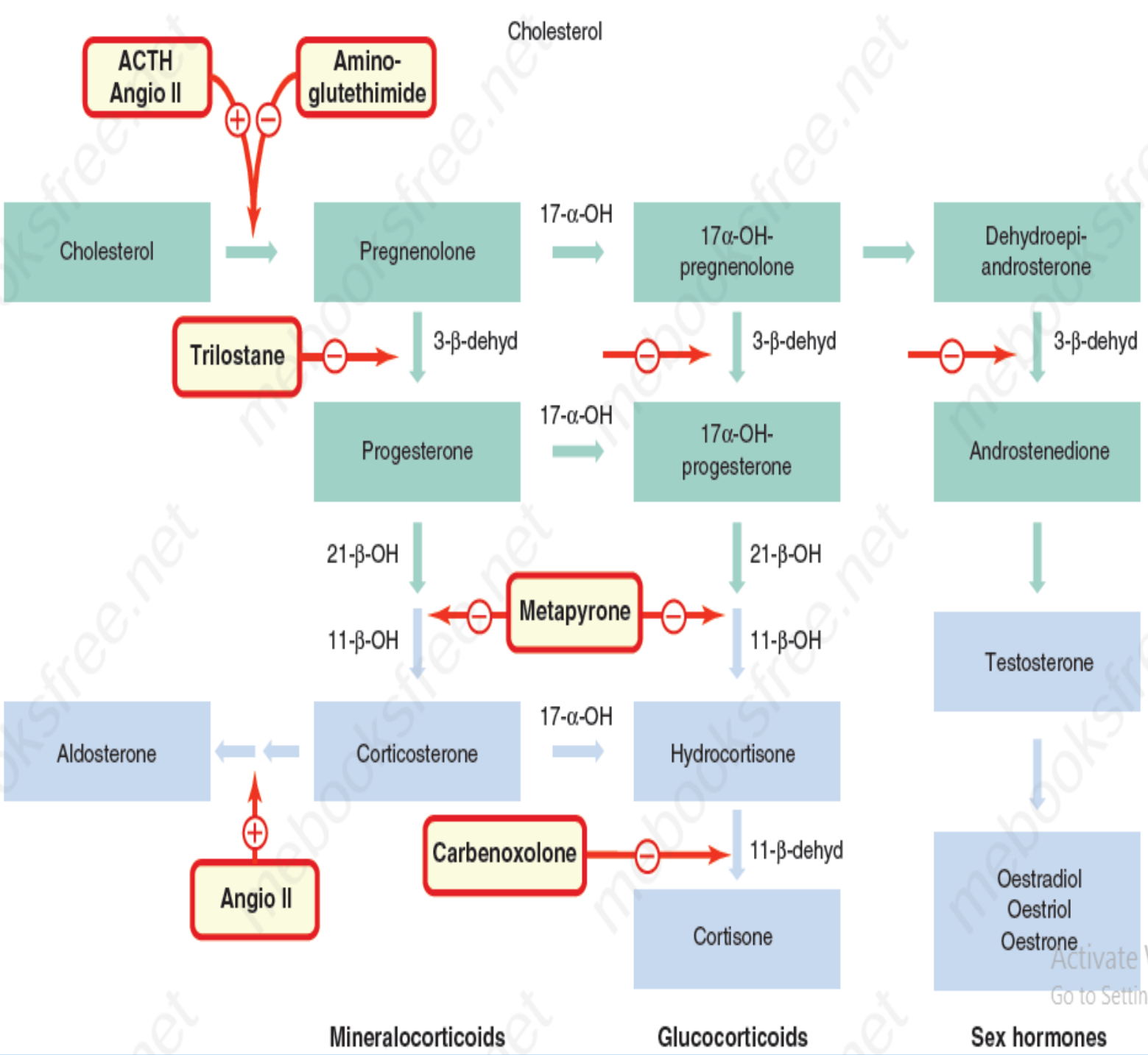
- Glucocorticoids are not stored in the adrenal gland.

- Corticotrophin-releasing factor **(CRF)** releases **adrenocorticotrophic hormone (ACTH, corticotrophin)** ,that stimulate the adrenal cortex to synthesize **corticosteroids**

- The release of both ACTH and CRF, in turn, is inhibited by the ensuing rising concentrations of glucocorticoids in the blood >>>>>

Negative Feed Back

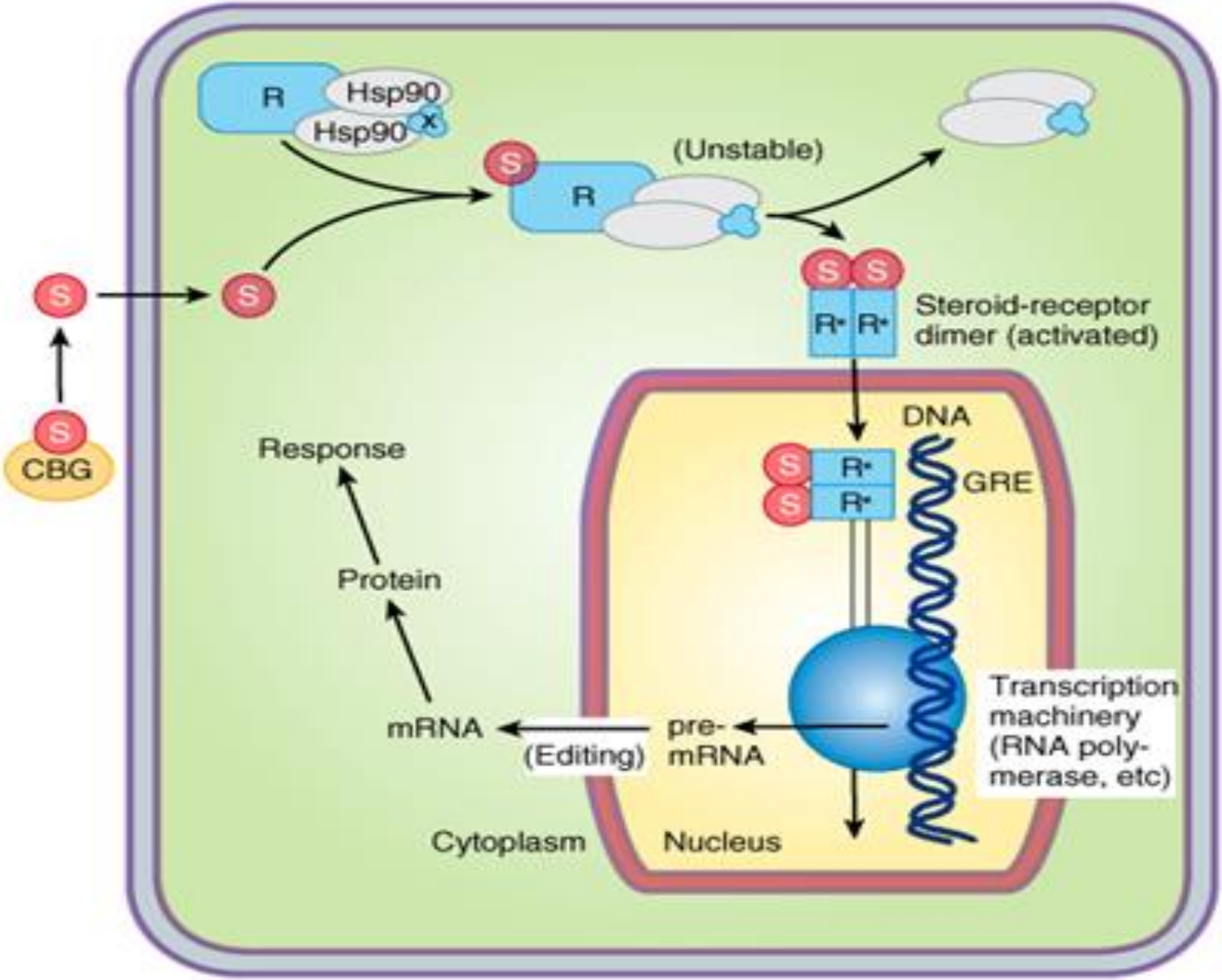
- The precursor of glucocorticoids is cholesterol. Which is converted to *pregnenolone>>>>>> rate-limiting step* ***regulated*** **by ACTH.**



MECHANISMS FOR GLUCOCORTICOID ACTION

- Interact with **specific receptor** proteins in target tissues to regulate the expression of **corticosteroid-responsive genes**, thereby changing the levels of proteins synthesized by the various target tissues.

- The receptors for corticosteroids are members of the **nuclear receptor** family.


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

- Some glucocorticoid actions occurs in minutes and cannot be accounted for by changes in protein synthesis.????

OTHER MECHANISMS :

- Interaction of the receptor with the regulatory complex, NF-κB.

- Protein kinases/phosphatase signalling systems.

  (e.g. liganded glucocorticoid receptor-induced phosphorylation by PKC and subsequent release of the protein *annexin-1 also known as lipocortin*, *which has potent* anti-inflammatory actions).

GLUCOCORTICOIDS ACTIONS

1. Metabolic actions .
2. Immunosuppressive and Anti-inflammatory actions.

1. METABOLIC ACTIONS :

- Glucocorticoids stimulate **gluconeogenesis, decrease cloucose uptake ,**As a result, blood glucose rises.

- Inhibit protein synthesis in muscles , skin .

Fat redistribution

- Both **lipolysis and lipogenesis** are stimulated, with a net increase of fat deposition in certain areas (eg, the face and the shoulders and back).

- Decreased protein synthesis and increased protein breakdown particularly in muscles.

- Also Catabolic effect skin, and lymphoid tissue .

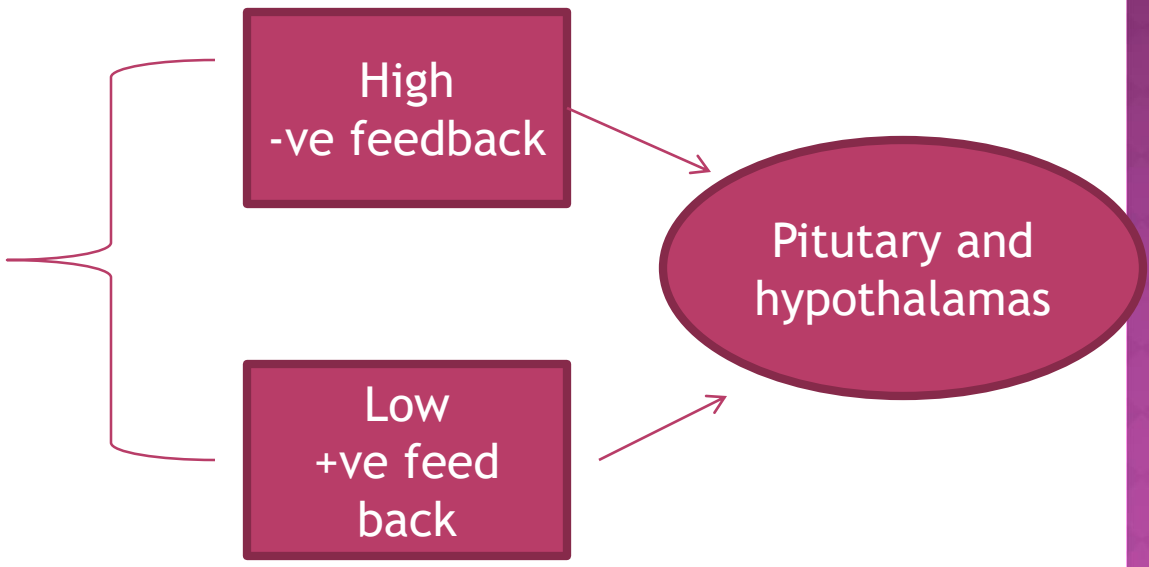
Osteoporosis

- **In bone** increases resorption while decreases calcium re-absoroptin and absorption .

- In the kidneys , 11ß-hydroxysteroid dehydrogenase enzyme has protective effect against hydrocortisone by preventing it from acting on the mineralocorticoid receptors .

- In high, non-physiological concentrations, have some mineralocorticoid actions, causing Na+ retention and K+ loss – possibly by swamping the protective 11ß-hydroxysteroid dehydrogenase enzyme.

- Steroid level



2. IMMUNOSUPPRESSIVE AND ANTI -INFLAMMATORY ACTION ACTIONS

- Overall:
- Reduction in the activity of the innate and acquired immune systems. ☺ ☺ ☺

- But also diminution in the protective aspects of the inflammatory response and sometimes decreased healing. ☹ ☹ ☹

- In acute inflammation: decreased influx and activity of leukocytes.
- In chronic inflammation: decreased activity of mononuclear cells.
- In lymphoid tissues: decreased clonal expansion of T and B cells, and decreased action of cytokine secreting T cells.

- Decreased production and action of many proinflammatory cytokines.
- Reduced generation of eicosanoids;
- Decreased generation of IgG
- Decrease in complement components in the blood.
- Increased release of *anti-inflammatory factors such* as interleukin (IL)-10, IL-1ra and annexin 1.

IMPORTANT GLUCOCORTICOIDS

- **A) Natural :<u>Cortisol</u>**—The major natural glucocorticoid , The physiologic secretion of **cortisol** is regulated by adrenocorticotropin **(ACTH).**

- Has slat retaining effect.
- Has short duration of action.
- Well absorbed when given orally.

- **B) Synthetic:**
- prednisone and , prednisolone, dexamethasone, and triamcinolone … etc

- Have longer duration of action .
- Lower salt retaining effect .
- Better penetration of lipid barriers for topical activity

CLINICAL USES

1. Adrenal disorders(replacement therapy):

- Glucocorticoids are essential to preserve life in patients with chronic adrenal cortical insufficiency (Addison's disease) and are necessary in acute adrenal insufficiency associated with life-threatening shock.

- *Addison's disease, is characterised by low* blood pressure, depression, anorexia, loss of weight and hypoglycaemia.

- Addison's disease may have an autoimmune aetiology, or it may be secondary to destruction of the gland by chronic inflammatory conditions such as tuberculosis.

- **2. Nonadrenal disorders**

(Anti-inflammatory/immunosuppressive):

- (eg, asthma, organ transplant rejection, collagen diseases, rheumatic disorders).

PHARMACOKINETICS

- **Routes of administration:**
- Oral
- Injectable
- Intra-articular.
- Aerosol directly into the respiratory tract.
- Nose or eye drops.
- Creams or ointments for application to the skin.
- Foam enemas for the GI tract.

- **Transport:**
- Endogenous glucocorticoids are transported in the plasma bound to *corticosteroid-binding globulin (CBG) and to albumin*.

- About 77% of plasma hydrocortisone is bound to CBG, but many synthetic glucocorticoids are not bound at all.

- **Metabolism:**
- Biological inactivation, which occurs in liver cells and elsewhere, is initiated by reduction of the C4–C5 double bond.

- Hydrocortisone has a plasma half-life of 90 min, although many of its biological effects have a latency of 2–8 h.

- Cortisone and **prednisone are inactive until converted in vivo by the** 11ß dehydrogenase type 1 to hydrocortisone and **prednisolone,** respectively.

Toxicity of Adrenocortical Steroids

Two categories of toxic effects result from the therapeutic use of corticosteroids:

1. Those resulting from withdrawal of steroid therapy.

2. Those resulting from continued use at supraphysiological doses.

Withdrawal of Therapy:

- A characteristic glucocorticoid withdrawal syndrome consists of:

fever, myalgias, arthralgias, and malaise, which may be difficult to differentiate from some of the underlying diseases for which steroid therapy was instituted.

TOXICITY

- Osteoprosis.
- Fat redistribuithion
- Moon face
- Cushing syndrome
- Hyperglycemia
- Reduce response to infection and injury.
- Muscle wasting.
- Sodium & water retention
- Inhibit growth in children
- Glucoma
- Adrenal suppression after prolonged use

For minimizing these toxicities :

- Local application (eg, aerosols for asthma).
- Alternate-day therapy (to reduce pituitary suppression).
- Tapering the dose soon after achieving a therapeutic response.

II) MINERALOCORTICOIDS

- **Aldosterone:** synthesis and release of aldosterone depends mainly on the electrolyte composition of the plasma and on the activity of the angiotensin II system.

- Low plasma Na+ or high plasma K+ concentrations directly stimulate aldosterone release.

- has short half - life.

- The most commonly used drug is **fludrocortisone** which can be taken orally.

MINERALO-CORTICOIDS MECHANISM OF ACTION

- They act on nuclear receptors. And exert change in gene transcription. (genomic action)
- Non genomic action (rapid)
- Their receptors are restricted to a few tissues, such as the kidney and the transporting epithelia of the colon and bladder.
- Cells containing mineralocorticoid receptors also contain the 11ß-hydroxysteroid dehydrogenase type 2 enzyme, which converts hydrocortisone (cortisol) into inactive cortisone, but does not inactivate aldosterone.

CORTICOSTEROID ANTAGONISTS

A) Receptor antagonists :

1. **<u>Mineralocorticod antagonist:</u>**
   Spironolactone and eplerenone, antagonists of aldosterone at its receptor.

2. **<u>Glucocorticoid antagonists:</u>**

Mifepristone is a competitive inhibitor of glucocorticoid receptors as well as progesterone receptors and has been used in the treatment of Cushing's syndrome.

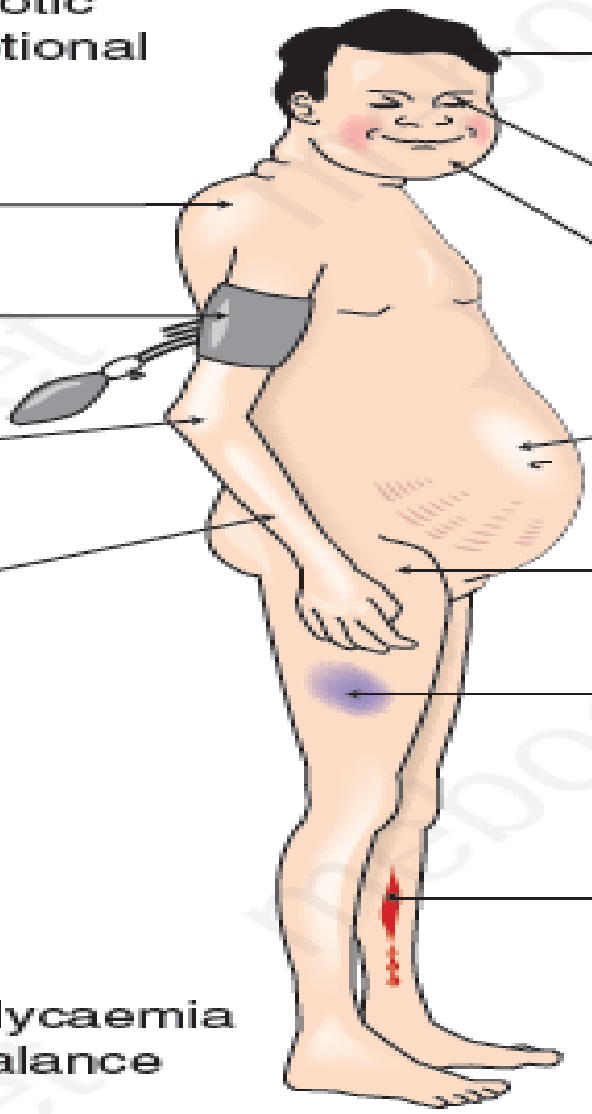
Euphoria
(though sometimes
depression or psychotic
symptoms, and emotional
lability)

Buffalo hump

(Hypertension)

Thinning
of skin

Thin arms
and legs:
muscle wasting



(Benign intracranial
hypertension)

(Cataracts)

Moon face, with red
(plethoric) cheeks

Increased
abdominal fat

(Avascular necrosis
of femoral head)

Easy bruising

Poor wound
healing

Also:
Osteoporosis
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
Increased susceptibility to infection
Obesity

B) Synthesis inhibitors

- **Metyrapone:** prevents the ß-hydroxylation at C11, and thus the formation of hydrocortisone and corticosterone (inactive)>>> could not produce –ve feedback >> so **it could be used to test the secretion of ACTH.**

- Also be used to treat patients with Cushing's syndrome.

- **Mitotane:** suppresses glucocorticoid synthesis by a direct (and unknown) mechanism on the adrenal gland. It is chiefly used to treat **adrenocortical carcinomas**.

- Other synthesis inhibitors include :
- **Ketoconazole**(which is antifungal) and **aminoglutethimide**

Compound	Relative affinity for GR	Approximate relative potency in clinical use		Duration of action after oral dose[a]	Comments
		Anti-inflammatory	Sodium retaining		
Hydrocortisone (cortisol)	1	1	1	Short	Drug of choice for replacement therapy.
Cortisone	0 (Prodrug)	0.8	0.8	Short	Inactive until converted to hydrocortisone; not used as anti-inflammatory because of mineralocorticoid effects.
Deflazacort	0 (Prodrug)	3	Minimal	Short	Converted by plasma esterases into active metabolite. Similar utility to prednisolone.
Prednisolone	2.2	4	0.8	Intermediate	Drug of choice for systemic anti-inflammatory and immunosuppressive effects.
Prednisone	0 (Prodrug)	4	0.8	Intermediate	Inactive until converted to prednisolone.
Methylprednisolone	11.9	5	Minimal	Intermediate	Anti-inflammatory and immunosuppressive.
Triamcinolone	1.9	5	None	Intermediate	Relatively more toxic than others.
Dexamethasone	7.1	27	Minimal	Long	Anti-inflammatory and immunosuppressive, used especially where water retention is undesirable (e.g. cerebral oedema); drug of choice for suppression of ACTH production.
Betamethasone	5.4	27	Negligible	Long	Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable.
Fludrocortisone	3.5	15	150	Short	Drug of choice for mineralocorticoid effects.
Aldosterone	0.38	None	500	N/A	Endogenous mineralocorticoid.

THANK YOU