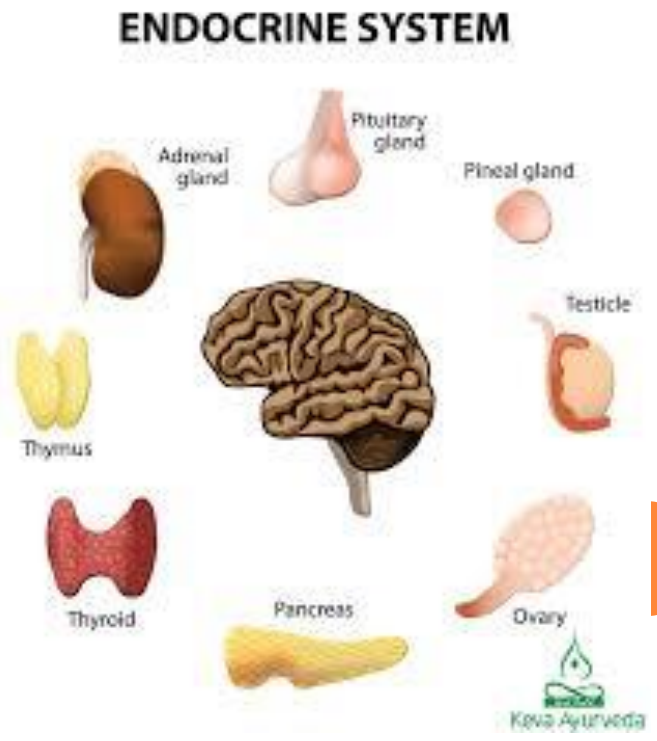
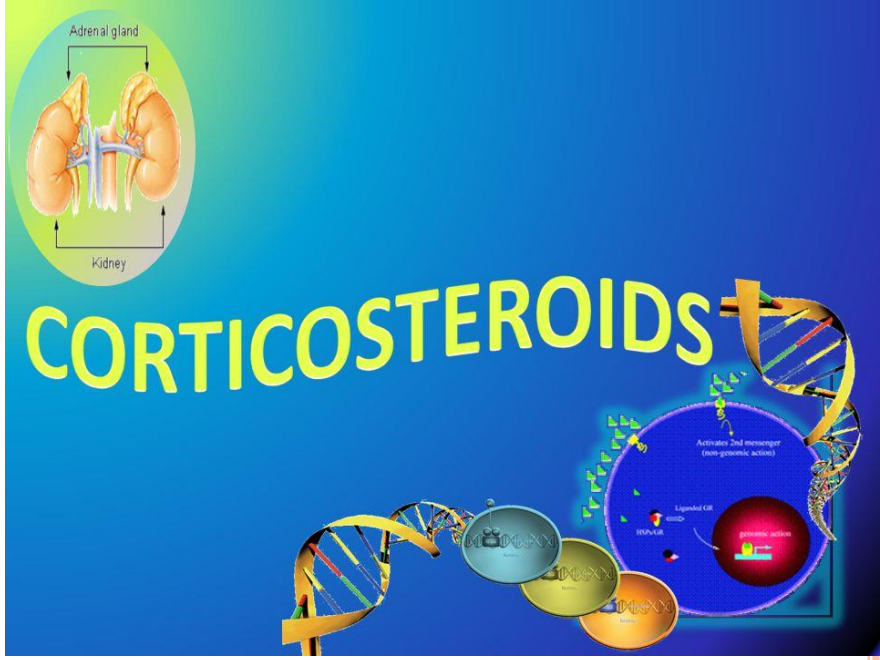
DRUGS ACTING ON ENDOCRINE SYSTEM

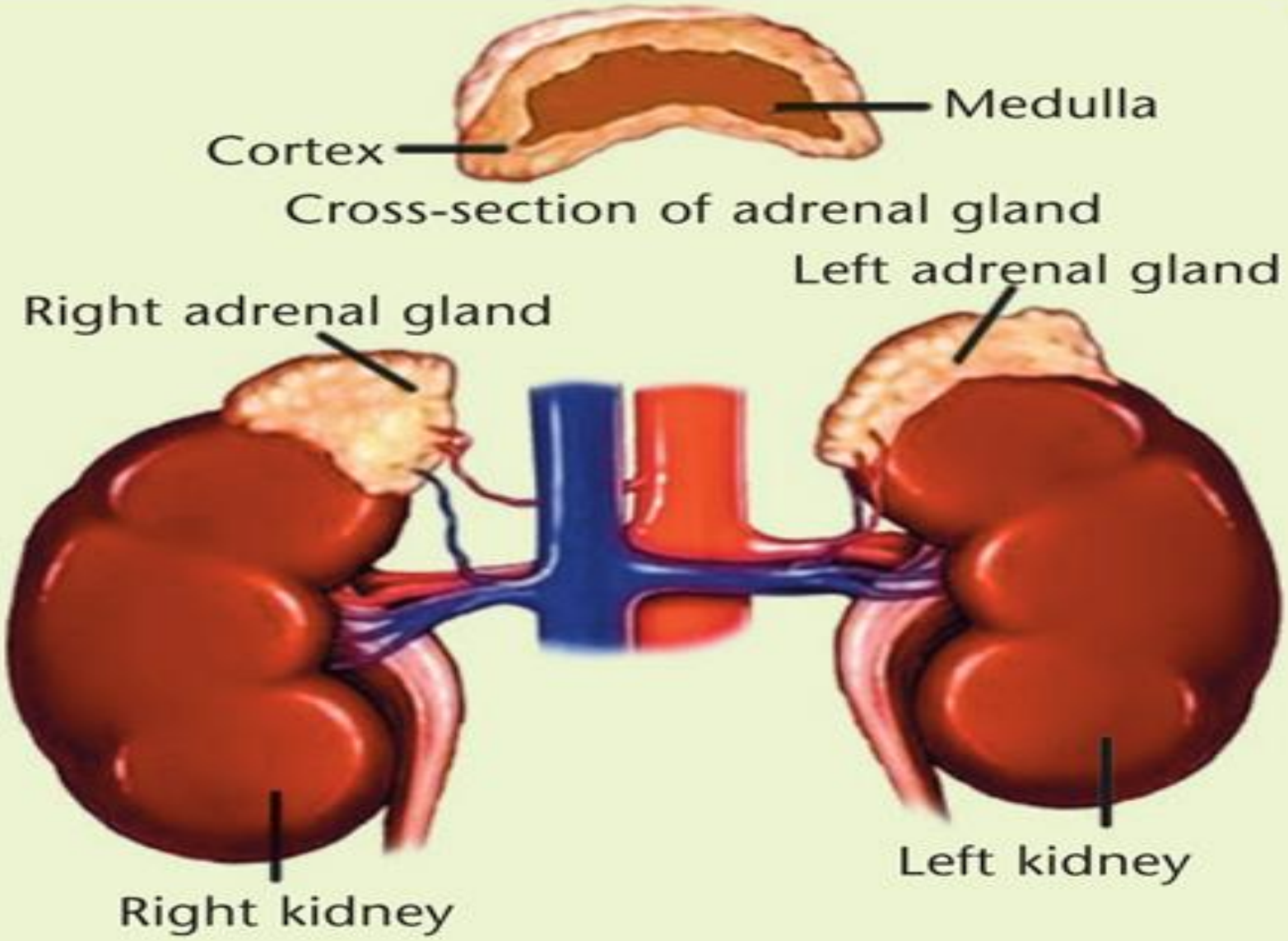




ADRENAL CORTICOSTEROIDS AND INHIBITORS

DR ASMA INAM
ASSOCIATE PROFESSOR
MBBS.MPHIL. PHD (1)

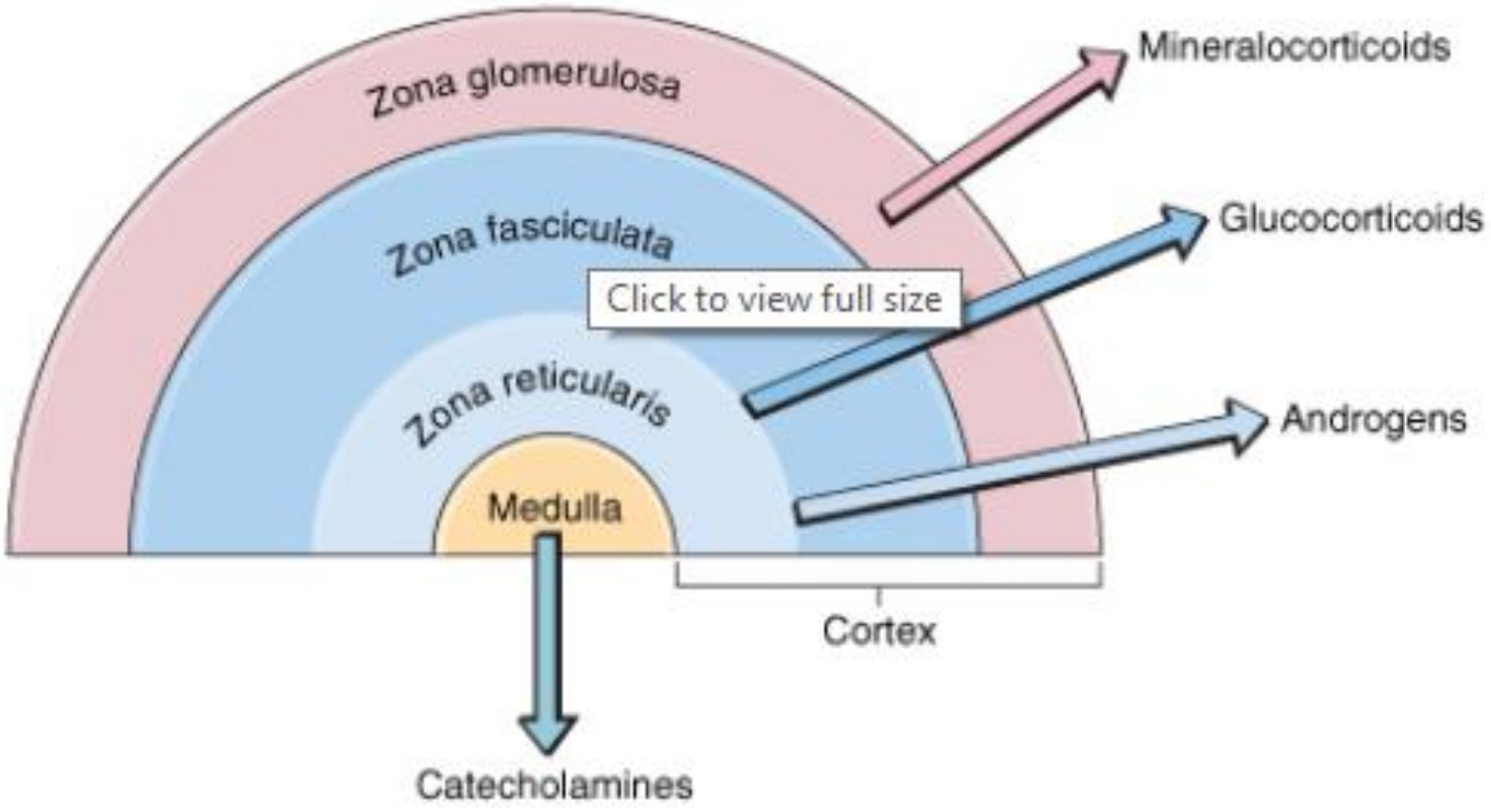
Figure 1. Adrenal glands[8]



- The adrenal gland consists of the cortex and the medulla.
- The medulla secretes:
- Epinephrine(Catecholamines)
- whereas the cortex, synthesizes and secretes two major classes of steroid hormones:
- ***adrenocorticosteroids (glucocorticoids and mineralocorticoids)***
- ***the adrenal androgens***.
- The adrenal cortex is divided into three zones that synthesize various steroids from cholesterol and then secrete them.

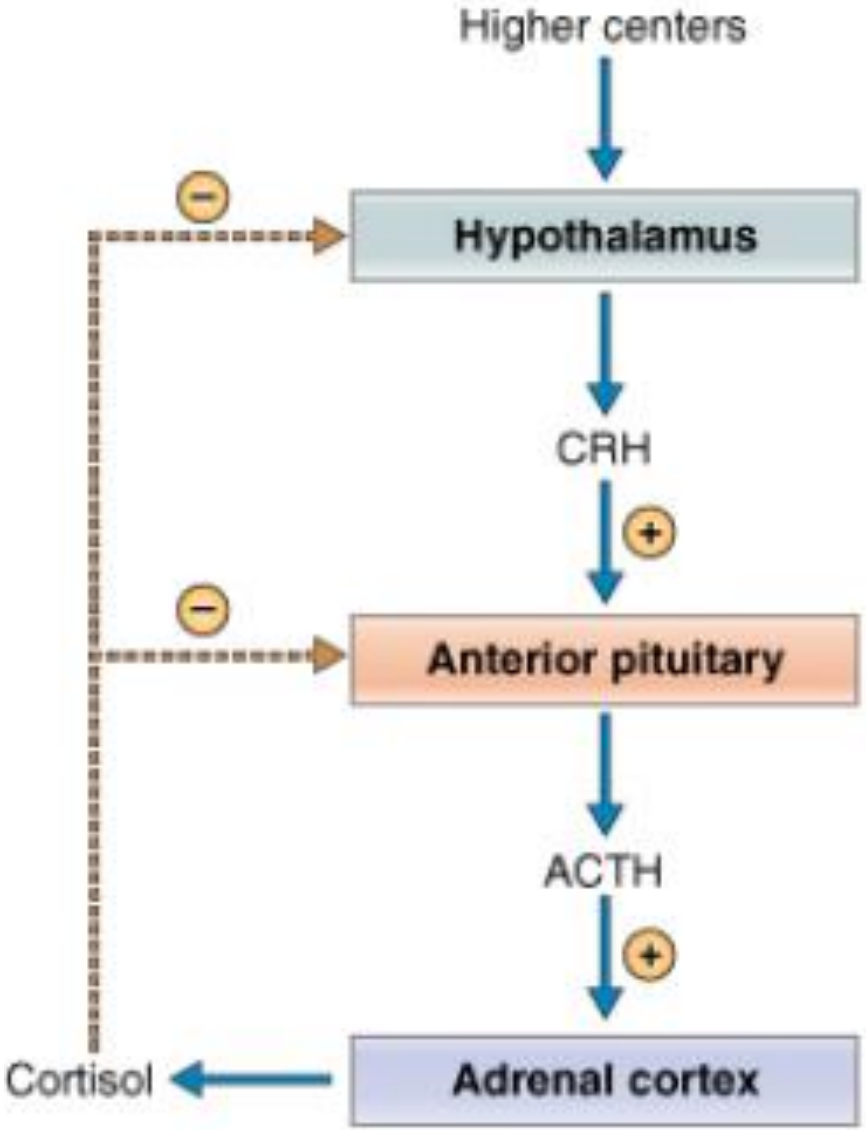
GLUCOCORTICOIDS
VERSUS
CORTICOSTEROIDS

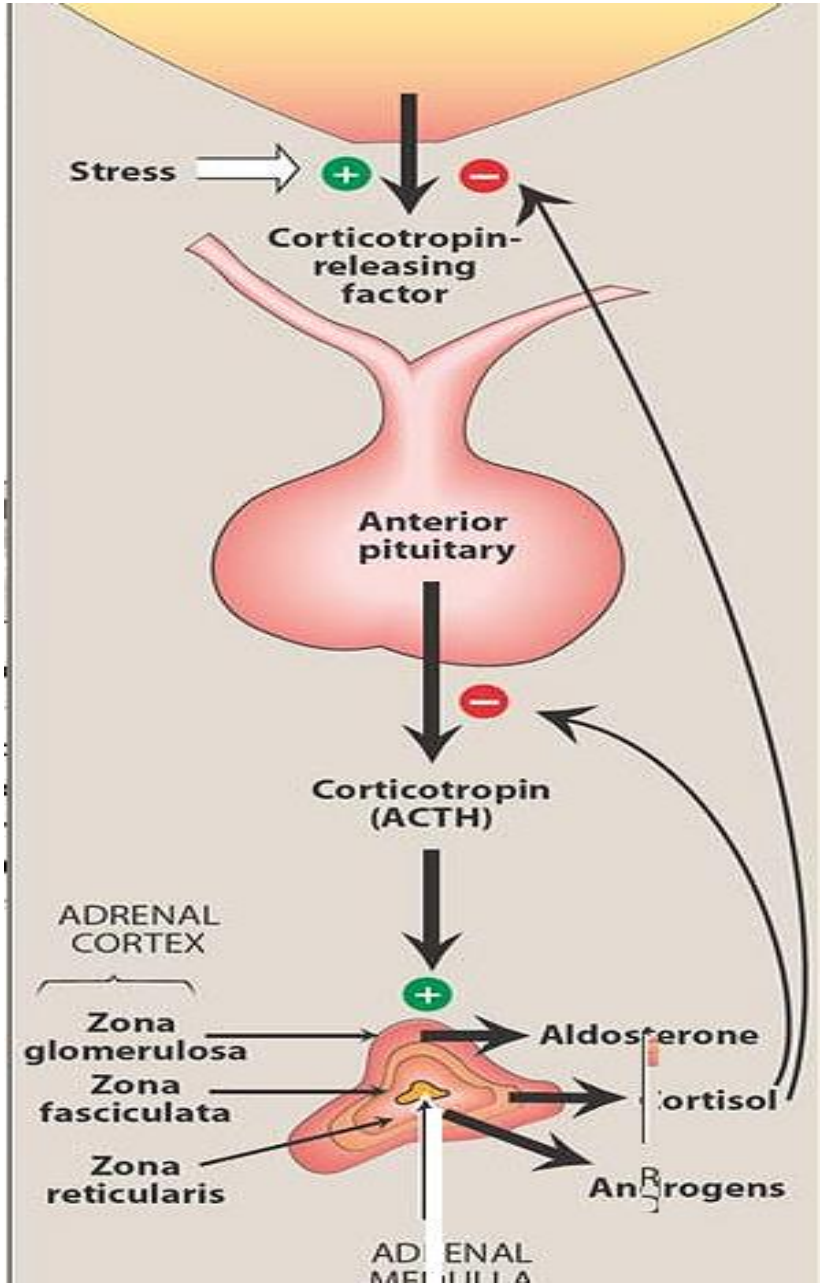
GLUCOCORTICOIDS	CORTICOSTEROIDS
The any of a group of corticosteroids involved in the metabolism of carbohydrates, proteins, and fats and have anti-inflammatory activity	Any of a group of steroid hormones produced in the adrenal cortex
One of the two types of corticosteroids	Types: Glucocorticoids and mineralocorticoids
Regulate carbohydrate, fat, and protein metabolism	Regulate a wide range of physiological processes

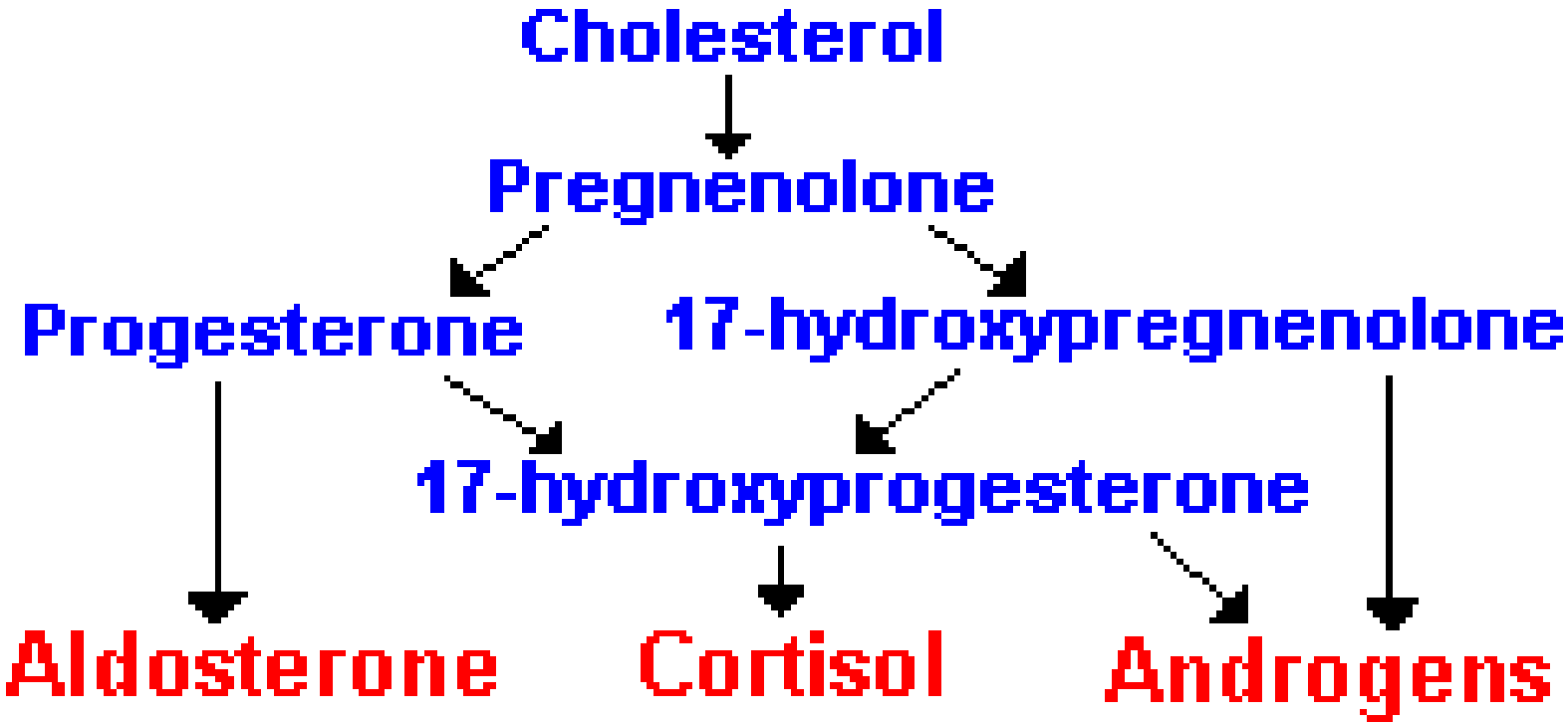


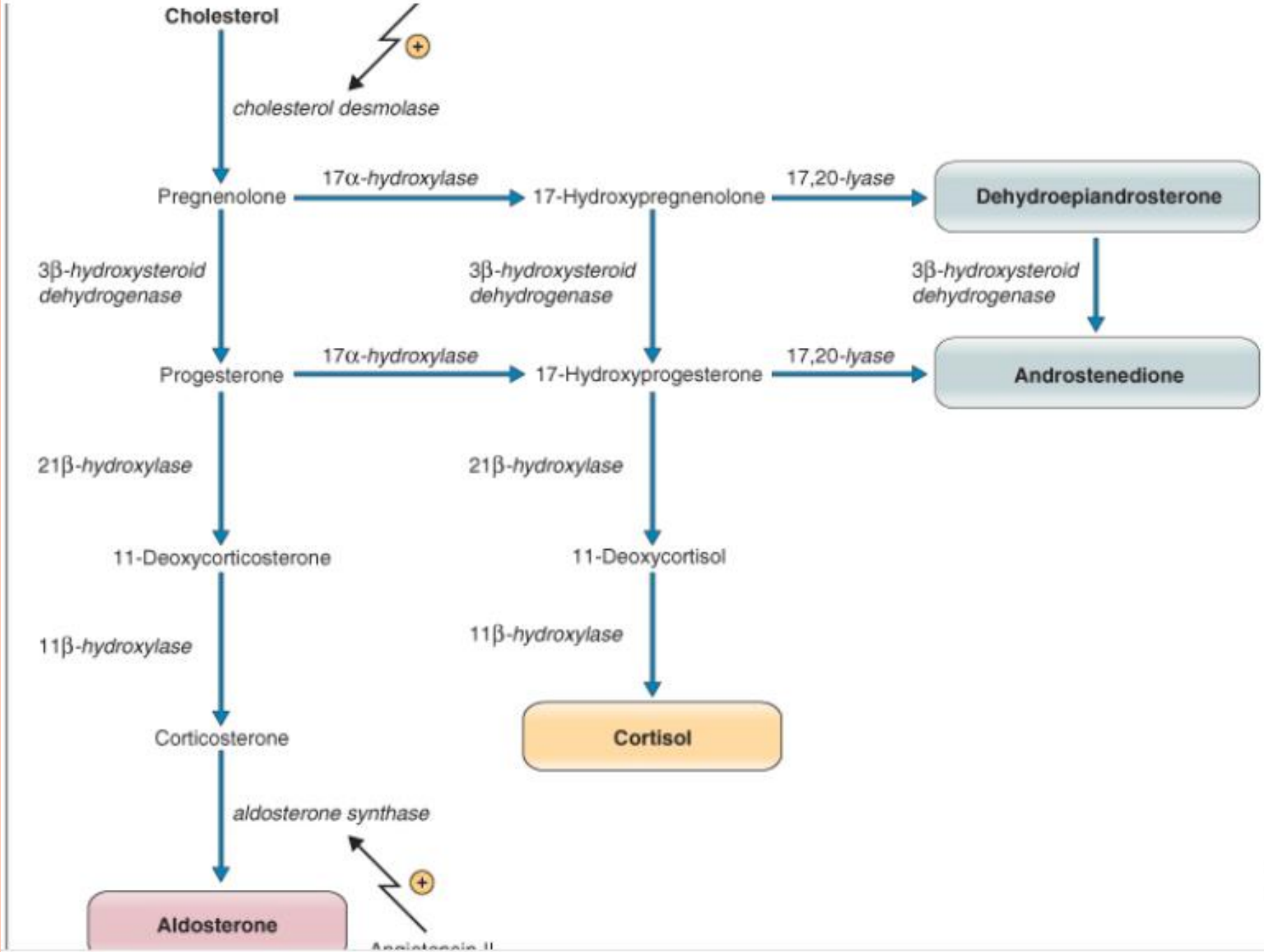
- The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone), which are responsible for regulating salt and water metabolism. Production of aldosterone is regulated primarily by the renin-angiotensin system .
- The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol), which are involved with normal metabolism and resistance to stress.

- The inner zona reticularis secretes adrenal androgens (for example, dehydroepiandrosterone).
- is controlled by pituitary corticotropin adrenocorticotropic hormone [ACTH; also called cortictropin], which is released in response to the hypothalamic corticotropin-releasing hormone (CRH; also called corticotropin-releasing factor).


Higher centers
Hypothalamus
CRH
Anterior pituitary
ACTH
Adrenal cortex
Cortisol


Stress
Corticotropin-releasing factor
Anterior pituitary
Corticotropin (ACTH)
ADRENAL CORTEX
Zona glomerulosa
Zona fasciculata
Zona reticularis
Aldosterone
Androgens


Cholesterol
Pregnenolone
Progesterone
17-hydroxypregnenolone
17-hydroxyprogesterone
Aldosterone
Cortisol
Androgens


Cholesterol
cholesterol desmolase
Pregnenolone
17α-hydroxylase
17-Hydroxypregnenolone
17,20-lyase
Dehydroepiandrosterone
3β-hydroxysteroid dehydrogenase
3β-hydroxysteroid dehydrogenase
3β-hydroxysteroid dehydrogenase
Progesterone
17α-hydroxylase
17-Hydroxyprogesterone
17,20-lyase
Androstenedione
21β-hydroxylase
21β-hydroxylase
11-Deoxycorticosterone
11-Deoxycortisol
11β-hydroxylase
11β-hydroxylase
Corticosterone
Cortisol
aldosterone synthase
Aldosterone

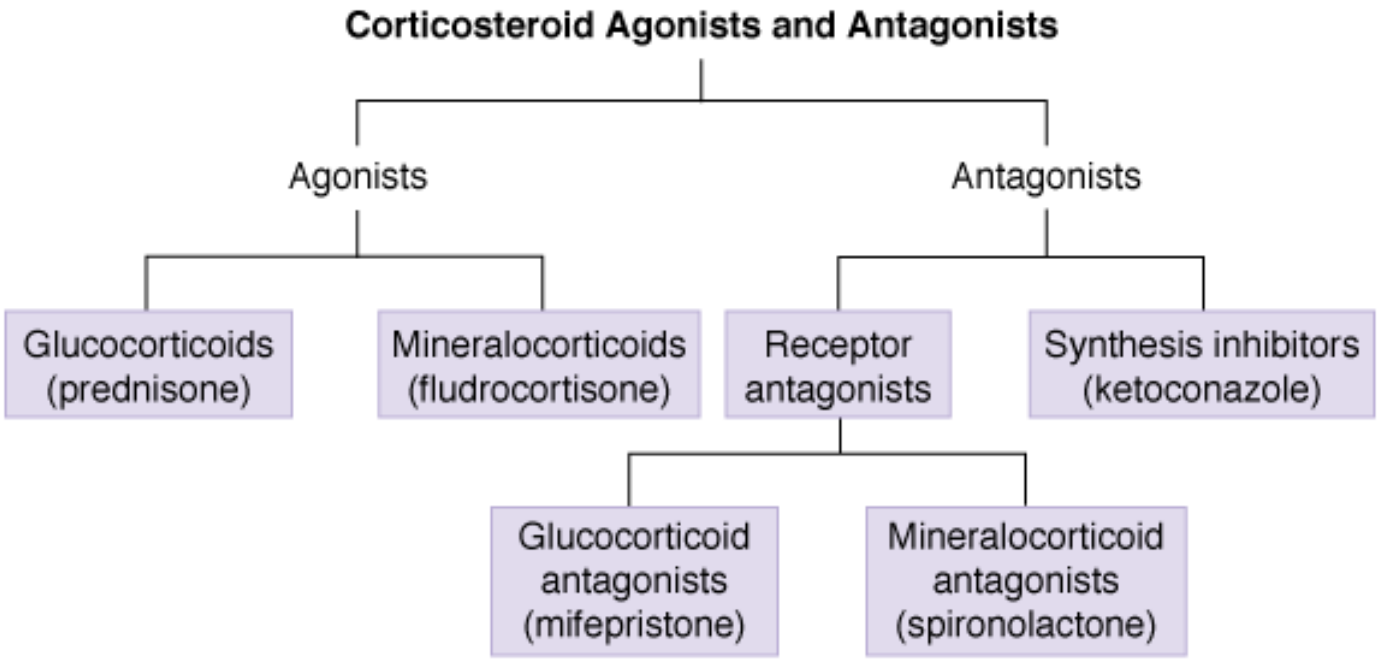
ADRENAL CORTICOSTEROIDS

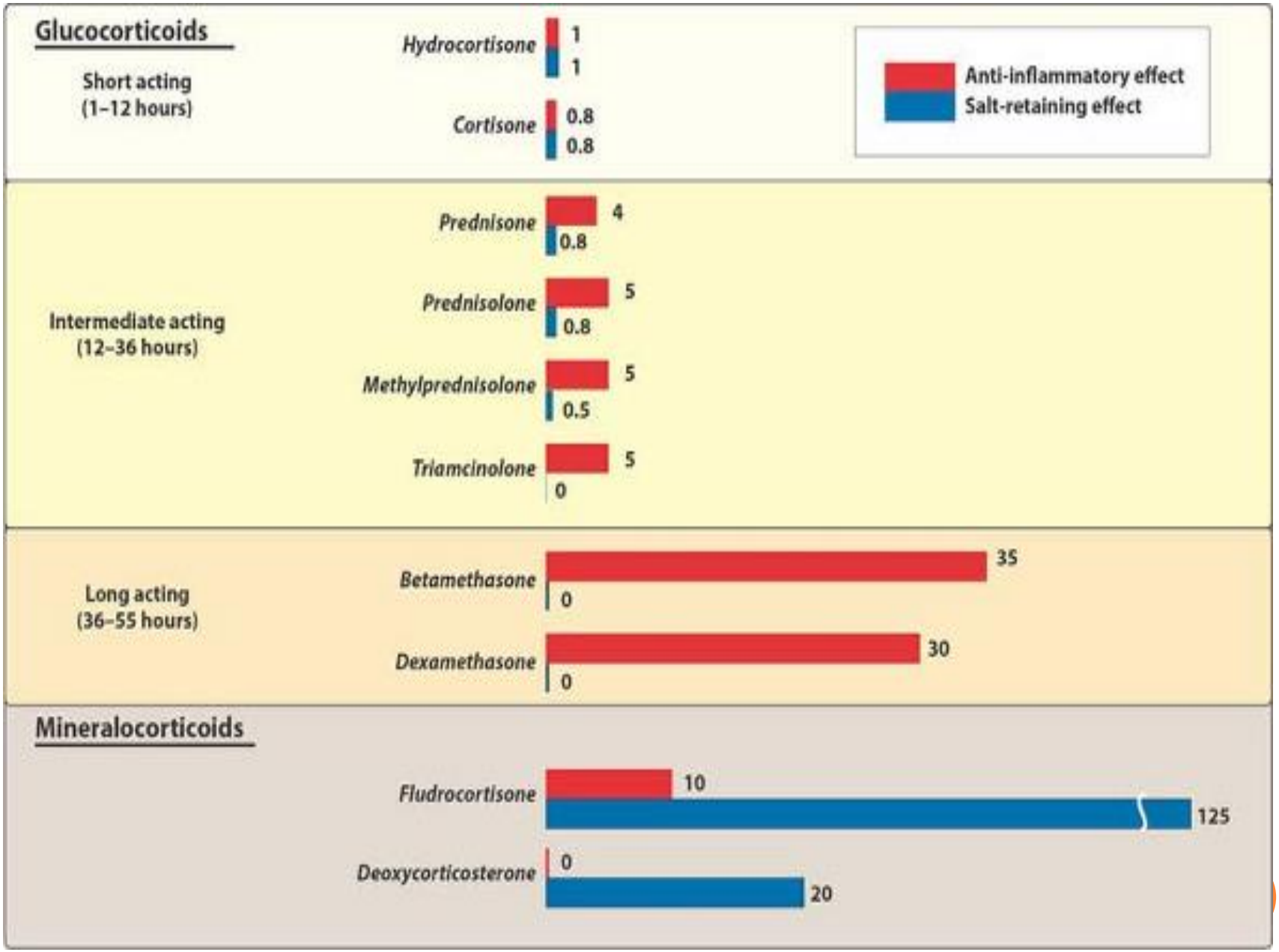
CORTICOSTEROIDS

- *Beclomethasone*
- *Betamethasone*
- *Cortisone*
- *Desoxycorticosterone*
- *Dexamethasone*
- *Fludrocortisone*
- *Hydrocortisone*
- *Methylprednisolone*
- *Prednisolone*
- *Prednisone*
- *Triamcinolone*

INHIBITORS OF ADRENOCORTICOID BIOSYNTHESIS OR FUNCTION

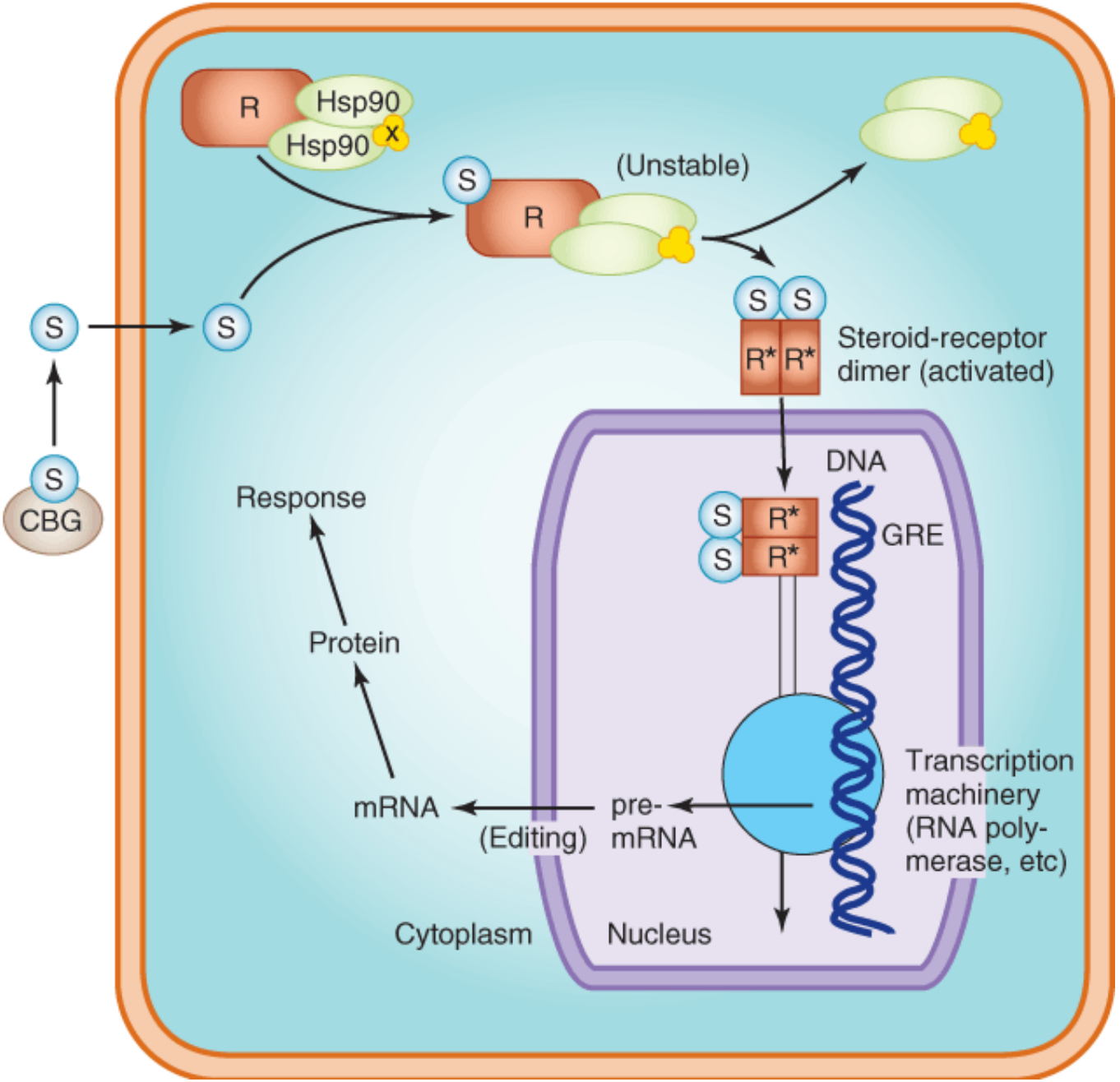
- *Aminoglutethimide*
- *Eplerenone*
- *Ketoconazole*
- *Metyrapone*
- *Mifepristone*
- *Spironolactone*
- *Trilostane*

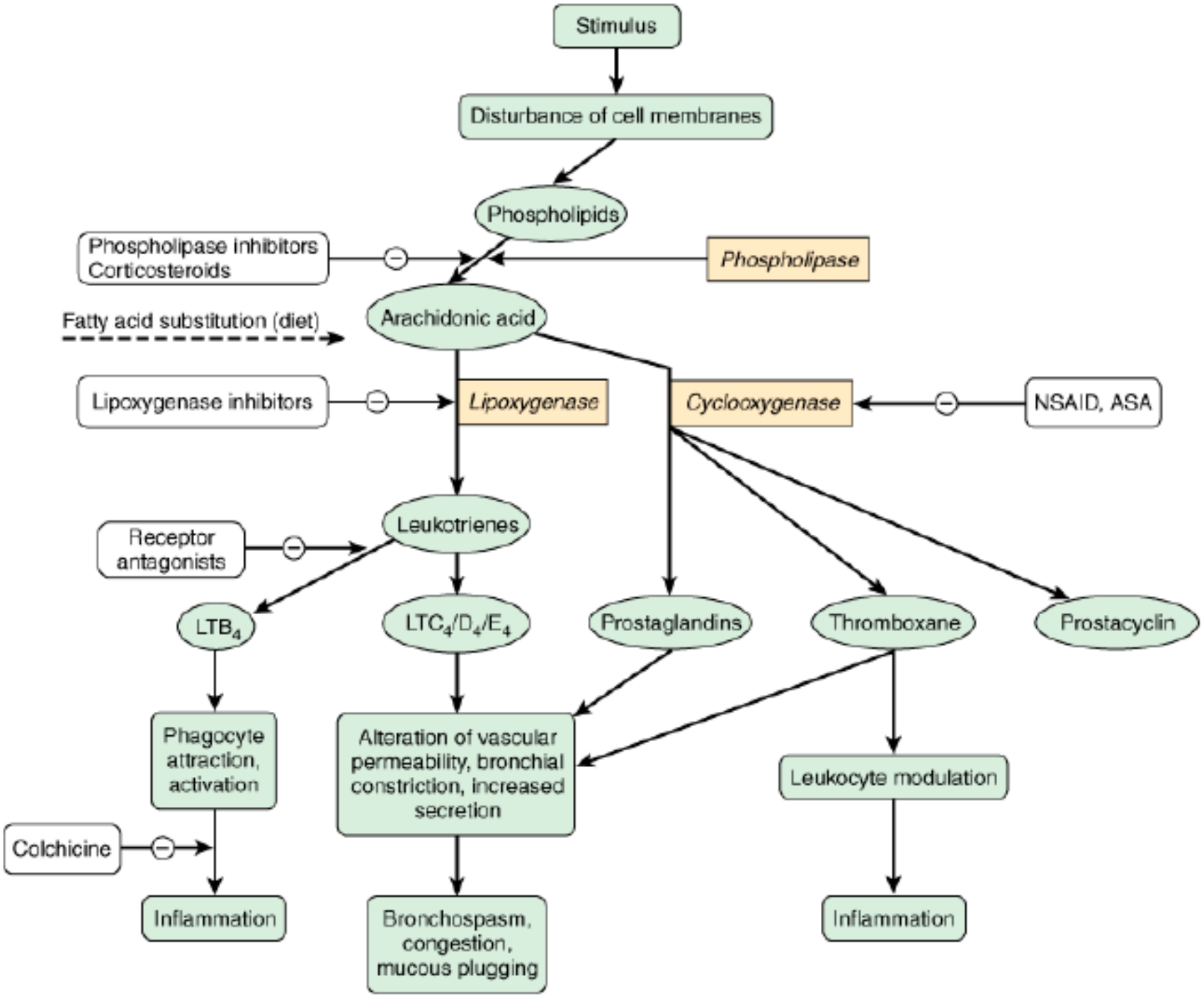

Corticosteroid Agonists and Antagonists
Agonists
Antagonists
Glucocorticoids (prednisone)
Mineralocorticoids (fludrocortisone)
Receptor antagonists
Synthesis inhibitors (ketoconazole)
Glucocorticoid antagonists (mifepristone)
Mineralocorticoid antagonists (spironolactone)


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
5
0.8
Methylprednisolone
5
0.5
Triamcinolone
5
0
Long acting
(36–55 hours)
Betamethasone
35
0
Dexamethasone
30
0
Mineralocorticoids
Fludrocortisone
10
125
Deoxycorticosterone
0
20

MECHANISM OF ACTION

- The adrenocorticoids bind to specific intracellular cytoplasmic receptors in target tissues.
- The glucocorticoid receptor is widely distributed throughout the body, whereas the mineralocorticoid receptor is confined mainly to excretory organs, such as the kidney, colon, and salivary and sweat glands.
- After dimerizing, the receptor-hormone complex translocates into the nucleus, where it attaches to gene promoter elements, acting as a transcription factor to turn genes on or off, depending on the tissue.


R
Hsp90
Hsp90
X
S
R
(Unstable)
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

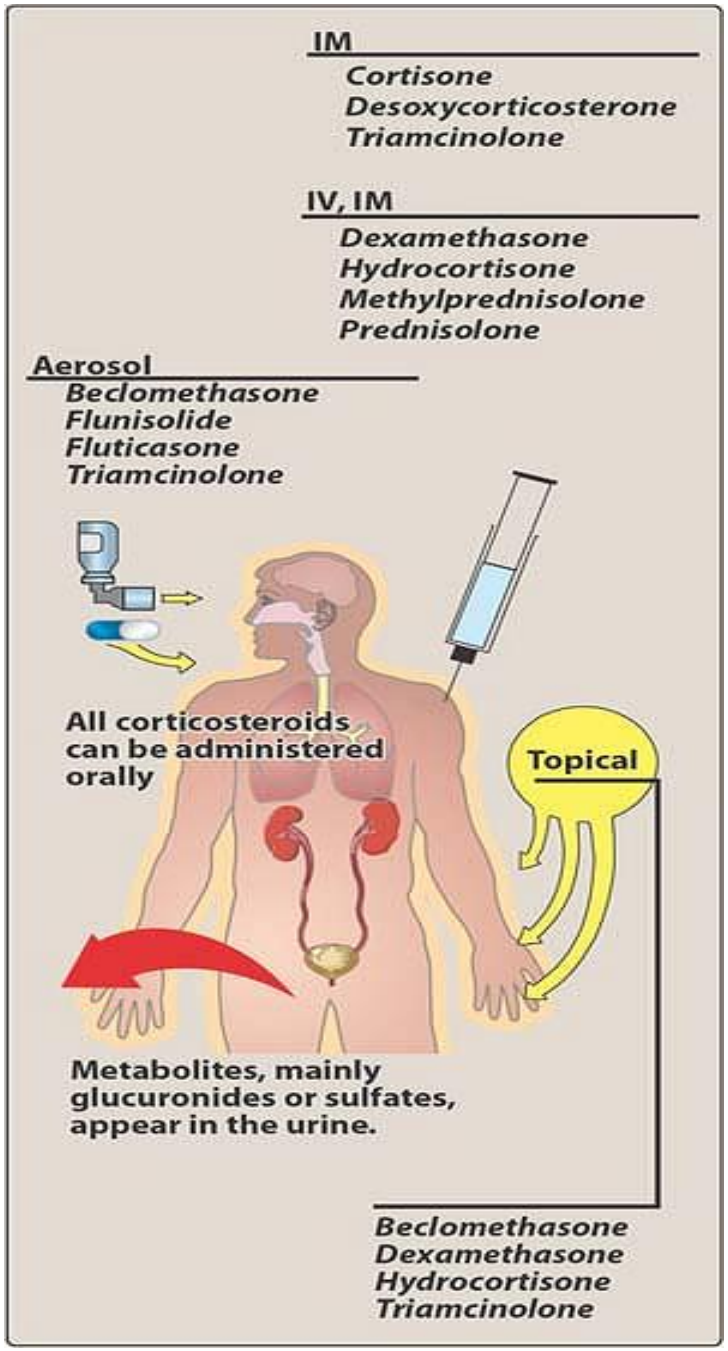

Stimulus
Disturbance of cell membranes
Phospholipids
Phospholipase inhibitors
Corticosteroids
Phospholipase
Fatty acid substitution (diet)
Arachidonic acid
Lipoxygenase inhibitors
Lipoxygenase
Cyclooxygenase
NSAID, ASA
Leukotrienes
Receptor antagonists
LTB4
LTC4/D4/E4
Prostaglandins
Thromboxane
Prostacyclin
Phagocyte attraction, activation
Alteration of vascular permeability, bronchial constriction, increased secretion
Leukocyte modulation
Colchicine
Inflammation
Bronchospasm, congestion, mucous plugging
Inflammation

Actions of glucocorticoids

- Stimulation of Gluconeogenesis
- Antiinflammatory action
- Suppression of immune response
- Maintenance of vascular response to Catecholamines
- Inhibition of bone formation
- Increase GFR
- CNS effects

Table 9-11. Actions of Adrenocortical Steroids

Actions of Glucocorticoids	Actions of Mineralocorticoids	Actions of Adrenal Androgens
Increase gluconeogenesis Increase proteolysis (catabolic)	Increase Na^+ reabsorption Increase K^+ secretion	Females: stimulate growth of pubic and axillary hair; stimu
Increase lipolysis	Increase H^+ secretion	Males: same as testosterone[Rx]
Decrease glucose[Rx] utilization		
Decrease insulin sensitivity		
Inhibit inflammatory response		
Suppress immune response		
Enhance vascular responsiveness to catecholamines		
Inhibit bone formation		
Increase GFR		
Decrease REM sleep		


IM
Cortisone
Desoxycorticosterone
Triamcinolone
IV, IM
Dexamethasone
Hydrocortisone
Methylprednisolone
Prednisolone
Aerosol
Beclomethasone
Flunisolide
Fluticasone
Triamcinolone
All corticosteroids can be administered orally
Topical
Metabolites, mainly glucuronides or sulfates, appear in the urine.
Beclomethasone
Dexamethasone
Hydrocortisone
Triamcinolone

ADVERSE EFFECTS

- Osteoporosis is the most common adverse effect due to the ability of glucocorticoids to suppress intestinal Ca^{2+} absorption, inhibit bone formation.
- The classic Cushing-like syndrome redistribution of body fat, puffy face, increased body hair growth, acne, insomnia, and increased appetite are observed when excess corticosteroids are present.
- Increased frequency of cataracts also occurs with long-term corticosteroid therapy.
- Hyperglycemia may develop and lead to diabetes mellitus. Diabetics should monitor their blood glucose and adjust their medications accordingly.
- Hypokalemia

N

Decreased growth in children

Osteoporosis

Increased risk of infection

Increased appetite

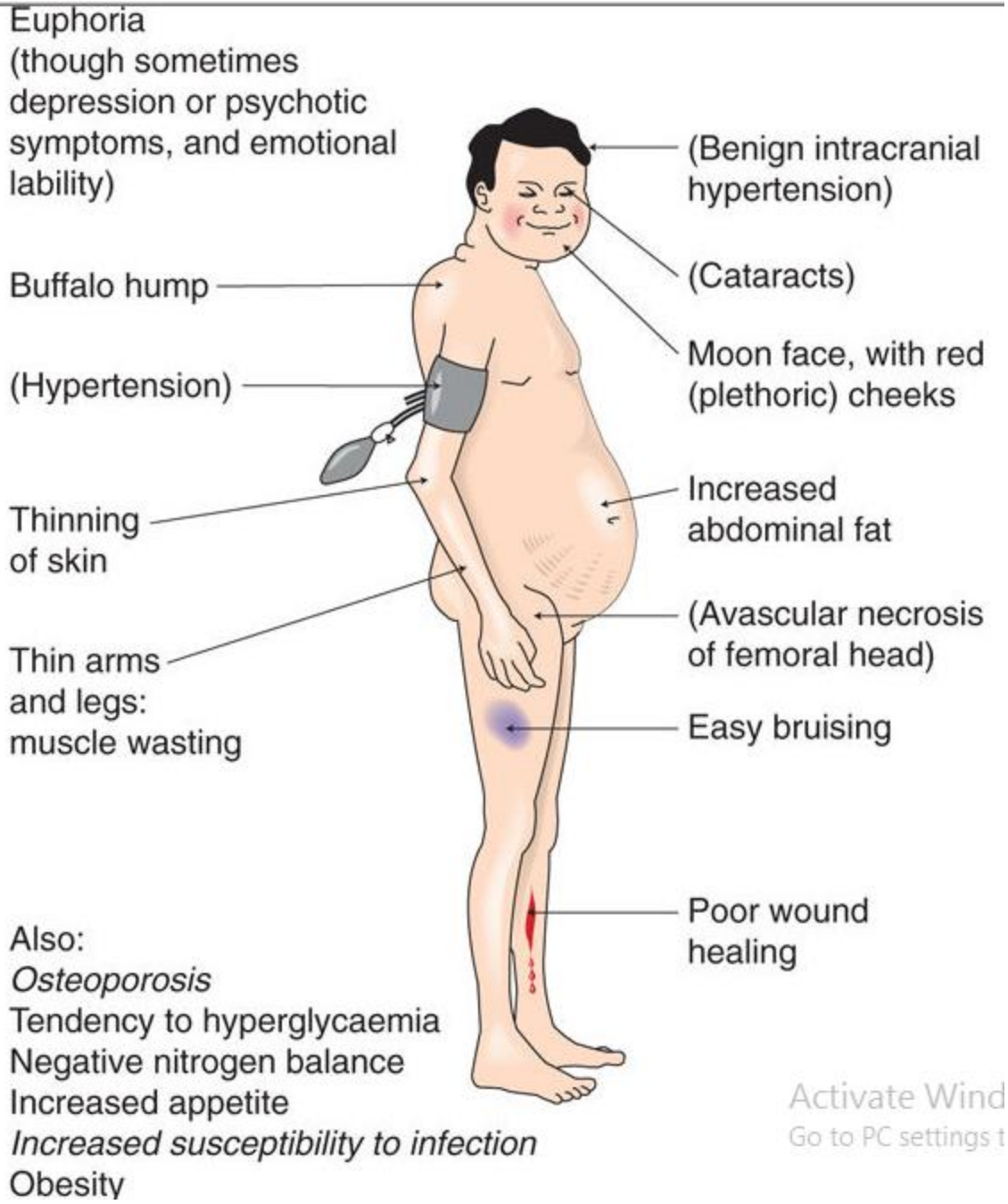
Emotional disturbances

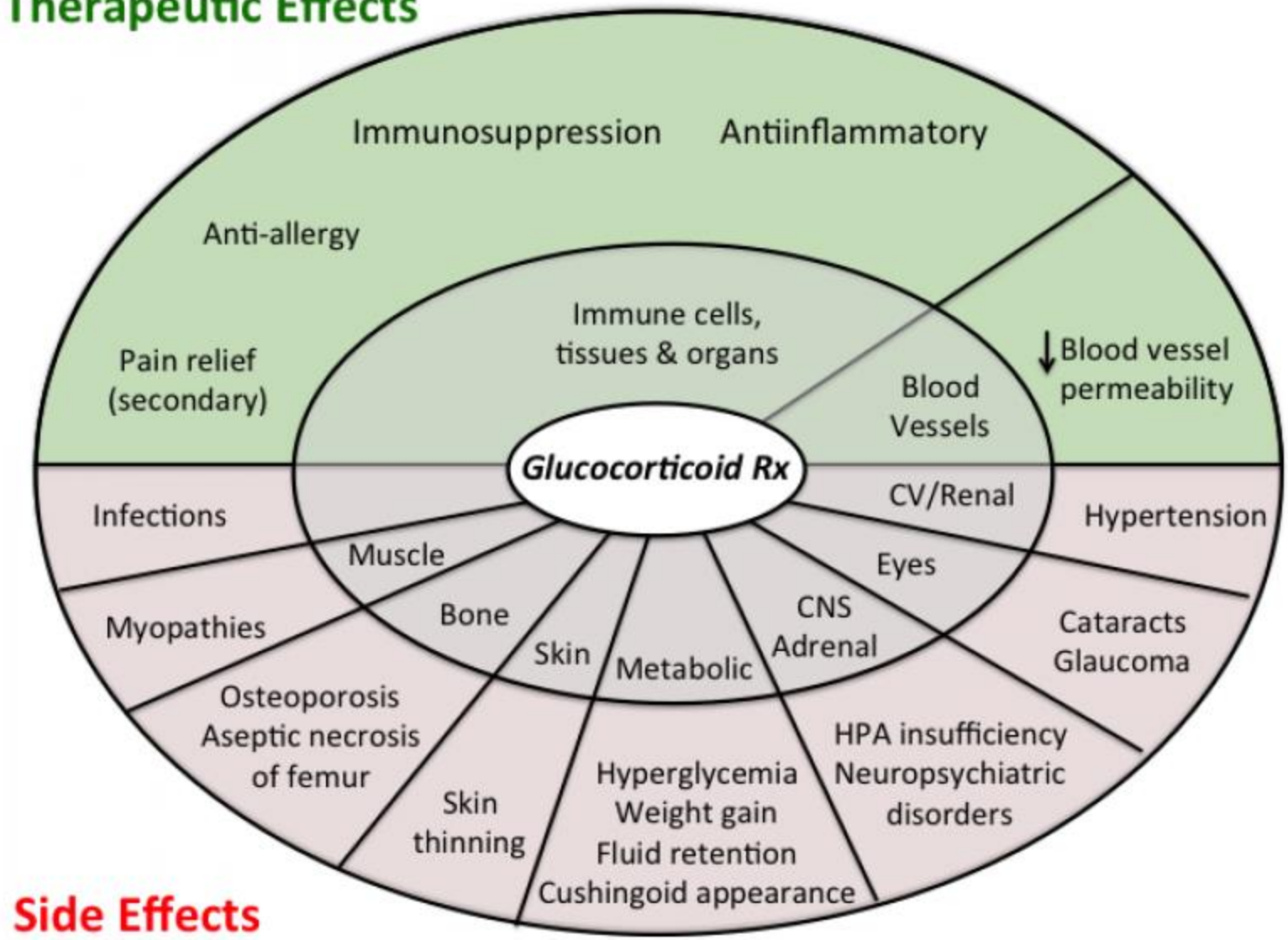
Hypertension

Peripheral edema

Peptic Ulcer

Glaucoma




Therapeutic Effects
Immunosuppression
Antiinflammatory
Anti-allergy
Pain relief
(secondary)
Immune cells,
tissues & organs
Blood vessel
permeability
Blood
Vessels
Glucocorticoid Rx
Infections
CV/Renal
Hypertension
Muscle
Eyes
Myopathies
Bone
CNS
Adrenal
Cataracts
Glaucoma
Skin
Metabolic
Osteoporosis
Aseptic necrosis
of femur
HPA insufficiency
Neuropsychiatric
disorders
Skin
thinning
Hyperglycemia
Weight gain
Fluid retention
Cushingoid appearance
Side Effects

To be completed by healthcare professional and kept by you

High Dose Inhaled Corticosteroid Safety Card

Name: ..... DOB: .....

I take: ..... Strength: .....

MDI + Spacer / Accuhaler / Turbohaler / .....

At a dose of: ..... puffs ..... time(s) a day

I may be at risk of corticosteroid insufficiency when I am ill and supplementation should be considered.

Prescriber: ..... Date: .....

Please peel off card


NDC 0781-5022-07
MethylPREDNIsolone
Tablets, USP
4 mg
℞ only
Unit of Use 21 Tablets
SANDOZ
SANDOZ
Dosage Directions
To remove tablet, press from this side.
1st day
2nd day
3rd day
4th day
5th day
6th day
MethylPREDNIsolone
Tablets, USP
4 mg
SANDOZ

THERAPEUTIC USES

- ***Adrenal uses***
- ***Replacement therapy for primary adrenocortical insufficiency (Addison's disease***: This disease is caused by adrenal cortex dysfunction (as diagnosed by the lack of patient response to corticotropin administration).

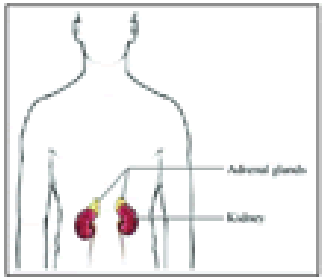
Hydrocortisone, which is identical to natural cortisol, is given to correct the deficiency.

- ***Replacement therapy for secondary or tertiary adrenocortical insufficiency***: These deficiencies are caused by a defect either in CRH production by the hypothalamus or in corticotropin production by the pituitary.

- ***Replacement therapy for congenital adrenal hyperplasia***: 21 b hydroxylase deficiency
- This is a group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones.
- This condition may lead to virilization in females due to overproduction of adrenal androgens (see below). Treatment of this condition requires administration of sufficient corticosteroids to normalize the patient's hormone levels by suppressing release of CRH and ACTH. This decreases production of adrenal androgens.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Normal Adrenal Gland

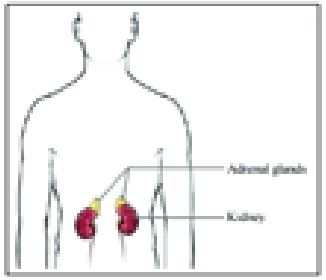


21-OH-Enzyme

Normal amount of Cortisol, Aldosterone and Androgen hormones

Normal Health and Sexual Development

Adrenal Gland in CAH



21-OH-Enzyme

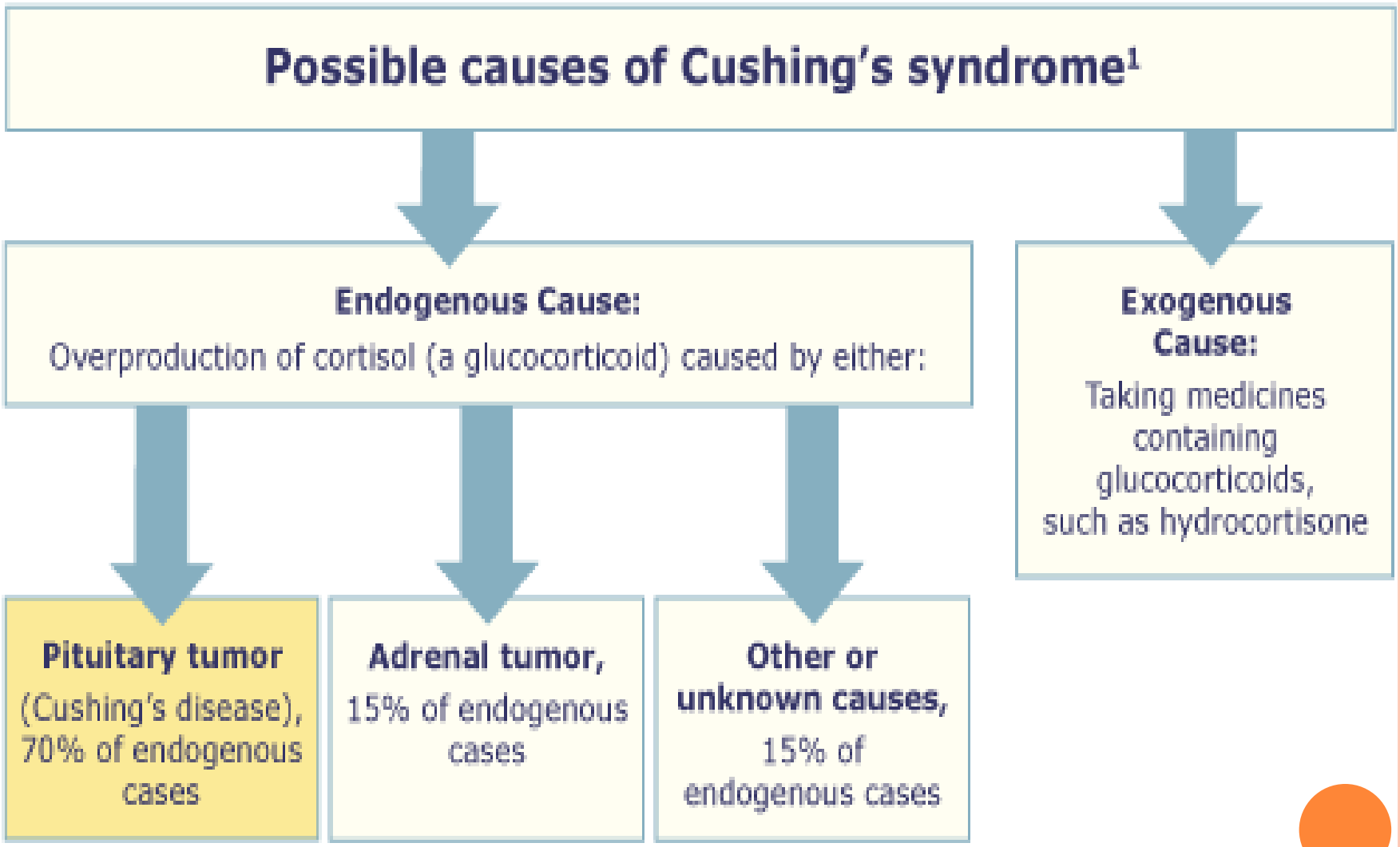
Decreased Cortisol and Aldosterone

Multiple Health Problems

Increased Androgens

Genital Changes, Early Puberty

- ***Diagnosis of Cushing's syndrome***:
- Cushing's syndrome is caused by a hypersecretion of glucocorticoids from an adrenal tumor or by exogenous administration .
- The dexamethasone suppression test is used to diagnose the cause of an individual's case of Cushing's syndrome.
- a synthetic glucocorticoid is administered, can distinguish between the two disorders


Possible causes of Cushing's syndrome[1]
Endogenous Cause:
Overproduction of cortisol (a glucocorticoid) caused by either:
Exogenous Cause:
Taking medicines containing glucocorticoids, such as hydrocortisone
Pituitary tumor
(Cushing's disease), 70% of endogenous cases
Adrenal tumor,
15% of endogenous cases
Other or unknown causes,
15% of endogenous cases

CUSHING'S DISEASE VS. CUSHING'S SYNDROME

Cushing's Disease	Cushing's Syndrome
More serious	Less serious
Caused by a pituitary tumor that secrets ACTH	Characterized by excessive levels of cortisol in the blood
Less common	More common
Develops due to abnormal tumor growth	Develops most often from taking meds that increase cortisol

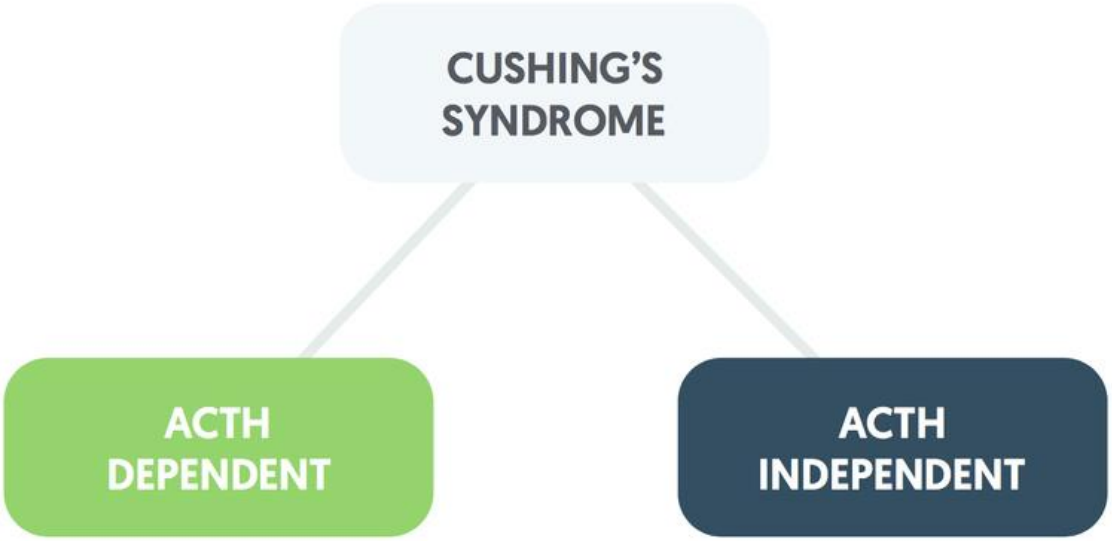
SIMILARITIES

Linked to stress, depression, poor diet, alcohol abuse, high amounts of estrogen or eating disorders

Small tumor growths appear in pituitary gland

Most of the same symptoms, including weight gain

Dr. Axe
FOOD IS MEDICINE



- Pituitary adenoma (Cushing's disease).
- Ectopic ACTH producing tumour (e.g. bronchial carcinoma).

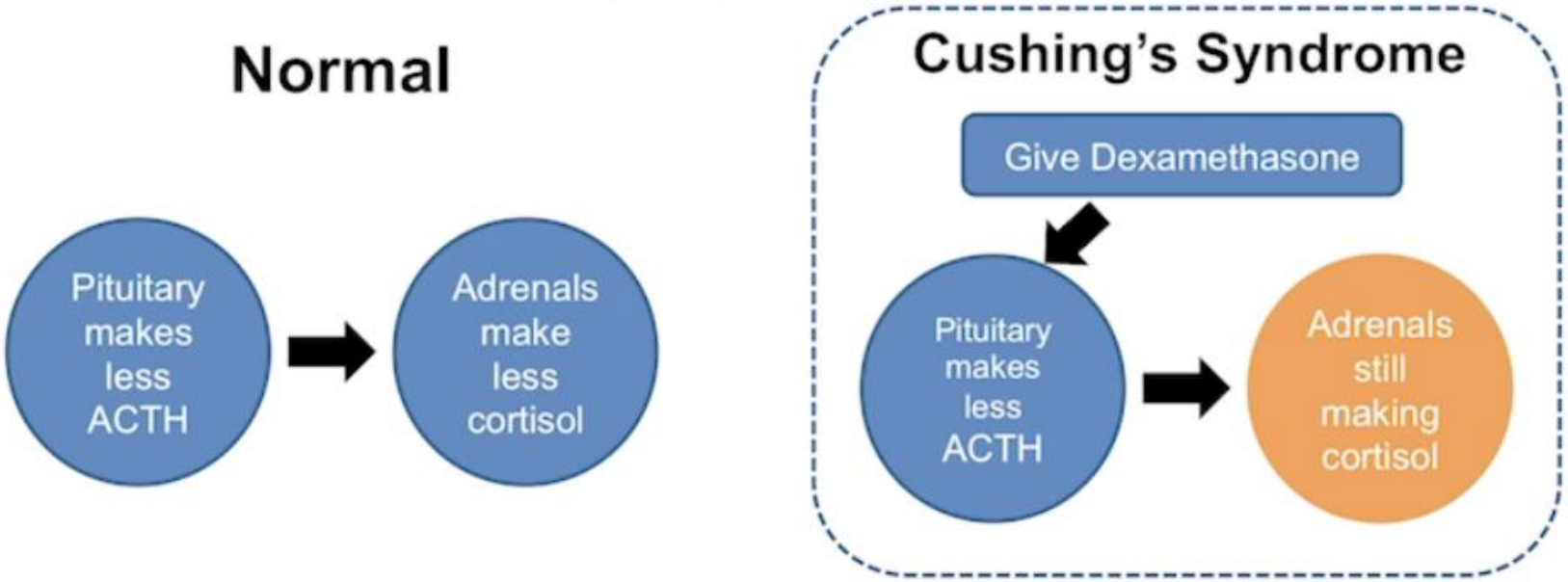
- Therapeutic corticosteroid administration
- Adrenal tumour (e.g. adrenal adenoma or carcinoma)

- . In Cushing's syndrome (primary adrenal defect with a normal CRH-ACTH axis), because the adrenal tumor functions autonomously, cortisol secretion is not suppressed by either low- or high-dose dexamethasone.

- In Cushing's disease, ACTH and cortisol secretion are suppressed by high-dose dexamethasone

Dexamethasone Suppression Test

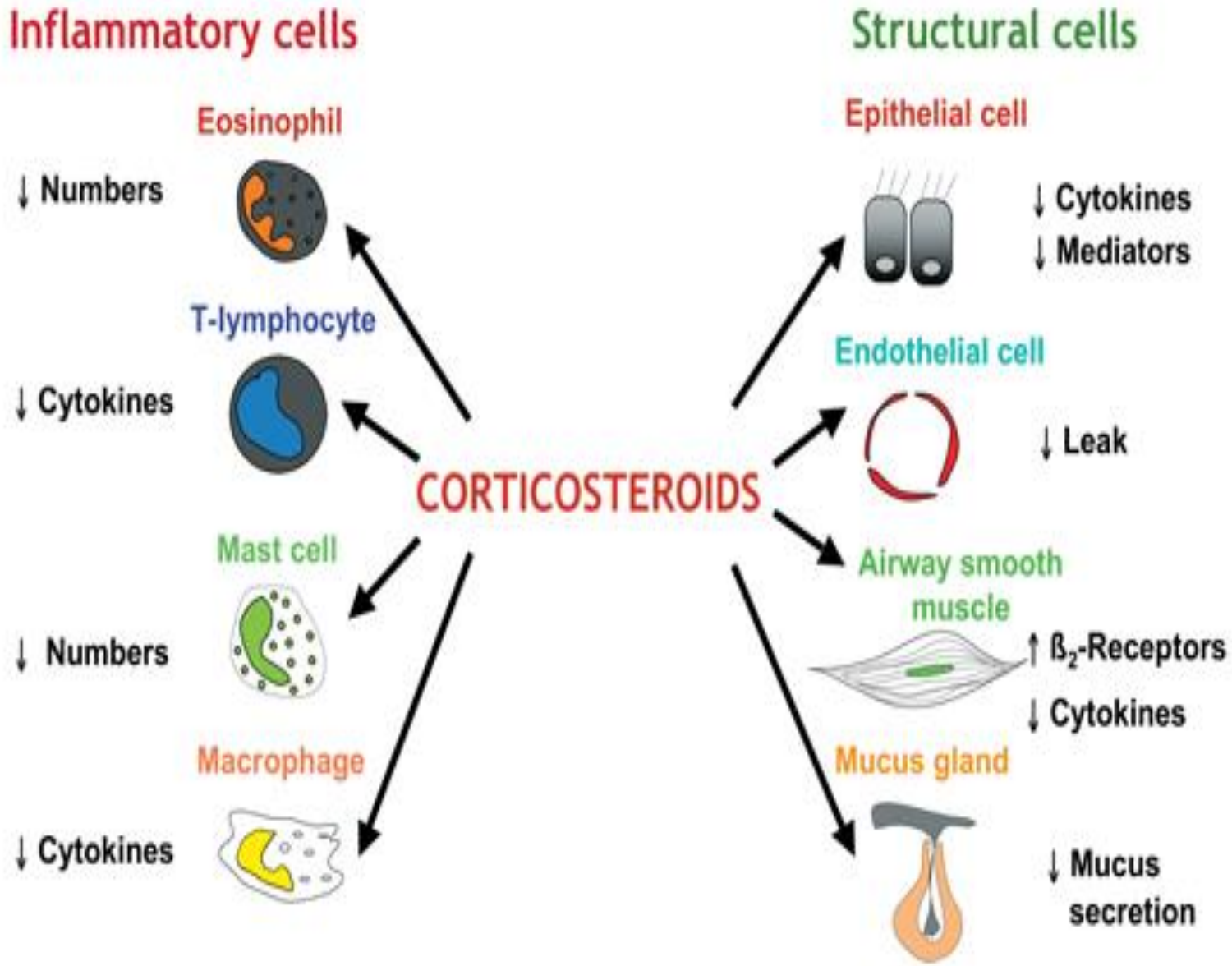
Dexamethasone acts like cortisol, lowers the amount of ACTH released by the pituitary gland

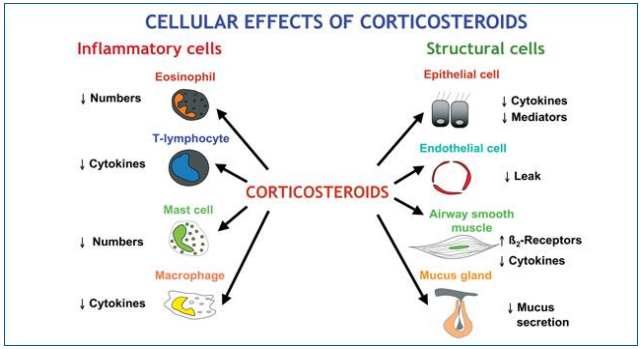


NON ADRENAL USES

- ***Relief of inflammatory symptoms***: Glucocorticoids dramatically reduce the manifestations of inflammations
- rheumatoid and osteoarthritic inflammations, as well as inflammatory conditions of the skin), including the redness, swelling, heat, and tenderness.
- The effect of glucocorticoids on the inflammatory process is the result of a number of actions, including the redistribution of leukocytes to other body compartments, thereby lowering their blood concentration.

CELLULAR EFFECTS OF CORTICOSTEROIDS





- Other effects include:
- an increase in the concentration of neutrophils
- a decrease in the concentration of lymphocytes (T and B cells), basophils, eosinophils, and monocytes
- inhibition of the ability of leukocytes and macrophages to respond to mitogens and antigens.
- The decreased production of prostaglandins and leukotrienes is believed to be central to the anti-inflammatory action

- ***Treatment of allergies***: Glucocorticoids are beneficial in the treatment of the symptoms of bronchial asthma, allergic rhinitis, and drug, serum, and transfusion allergic reactions.

- ***Acceleration of lung maturation***: Respiratory distress syndrome is a problem in premature infants. Fetal cortisol is a regulator of lung maturation

- hematopoietic cancers
- neurologic disorders
- chemotherapy-induced vomiting
- hypercalcemia
- mountain sickness

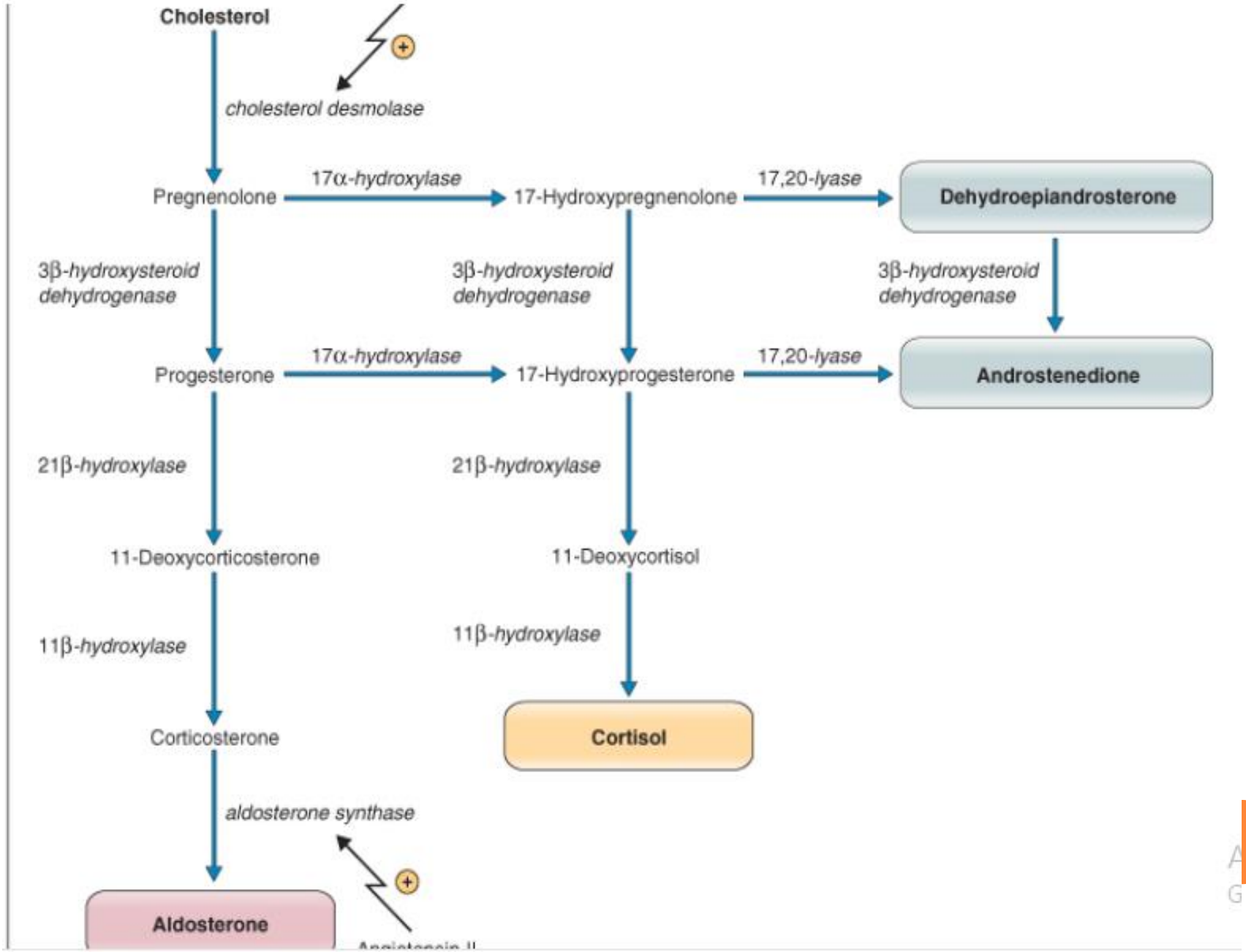
Inhibitors of adrenocorticoid biosynthesis

Metyrapone:

Metyrapone is used for tests of adrenal function and can be used for the treatment of pregnant women with Cushing's syndrome.

Metyrapone interferes with corticosteroid synthesis by blocking the final step (11-hydroxylation) in glucocorticoid synthesis, leading to an increase in 11-deoxycortisol as well as adrenal androgens and the potent mineralocorticoid 11-deoxycorticosterone.

The adverse effects encountered with metyrapone include salt and water retention, hirsutism, transient dizziness, and gastrointestinal disturbances.


Cholesterol
cholesterol desmolase
Pregnenolone
17α-hydroxylase
17-Hydroxypregnenolone
17,20-lyase
Dehydroepiandrosterone
3β-hydroxysteroid dehydrogenase
3β-hydroxysteroid dehydrogenase
3β-hydroxysteroid dehydrogenase
Progesterone
17α-hydroxylase
17-Hydroxyprogesterone
17,20-lyase
Androstenedione
21β-hydroxylase
21β-hydroxylase
11-Deoxycorticosterone
11-Deoxycortisol
11β-hydroxylase
11β-hydroxylase
Corticosterone
Cortisol
aldosterone synthase
Aldosterone

AMINOGLUTETHIMIDE

This drug acts by inhibiting the conversion of cholesterol to pregnenolone. As a result, the synthesis of all hormonally active steroids is reduced. Aminoglutethimide has been used therapeutically in the treatment of breast cancer to reduce or eliminate androgen and estrogen production

- **Ketoconazole:** Ketoconazole is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing's syndrome.

MIFEPRISTONE:

- At high doses, mifepristone is a potent glucocorticoid antagonist as well as an antiprogestin. Its use is presently limited to the treatment of inoperable patients with ectopic ACTH syndrome.

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. It is effective against hyperaldosteronism.
- Spironolactone is also useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle. Adverse effects include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

EPLERENONE:

- Eplerenone specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the side effect of gynecomastia that is associated with the use of spironolactone. It is approved as an antihypertensive

CORTICOSTEROID INHIBITORS AND ANTAGONIST

Drug	Mechanism of Action	Clinical Use
Corticosteroid synthesis inhibitors		
Aminoglutethimide	Reversible blockade of the conversion of cholesterol to pregnenolone (production of all adrenal steroids is inhibited)	➡ Cushing's syndrome ➡ Ovariectomized women with metastatic breast cancer (to eliminate adrenal estrogen production)
Ketoconazole (high doses)	Reversible blockade of several steps of steroidogenesis requiring cytochrome P450 enzymes	Cushing's syndrome
Receptor antagonists		
Mifepristone (high doses)	Blockade cytoplasmic glucocorticoid receptor	Inoperable patients with ectopic ACTH secretions or adrenal carcinoma (it is also an antiprogestin)
Spironolactone	Blockade of cytoplasmic mineralocorticoid receptor	➡ Hyperaldostronism ➡ Hirsutism in women

MCQs

1.Osteoporosis is a major adverse effect caused by the glucocorticoids. It is due to their ability to:

- A. Increase the excretion of calcium.
- B. Inhibit absorption of calcium.
- C. Stimulate the HPA axis.
- D. Decrease production of Prostaglandins

- **2. Measurements of cortisol precursors and plasma dehydroepiandrosterone sulfate confirm the diagnosis of congenital adrenal hyperplasia (CAH) in a child. This condition can be effectively treated by:**
- A. Suppressing the release of ACTH.
- B. Administering an androgen antagonist.
- C. Administering metapyrone to decrease cortisol synthesis.
- D. Removing the adrenal gland

- **3. A Child with asthma is being treated effectively with an inhaled preparation of beclomethasone dipropionate. Which of the following adverse effects is of particular concern?**
- A. Hypoglycemia.
- B. Hirsutism.
- C. Growth suppression.
- D. Cushing's syndrome.
- E. Cataract

4.A patient with Addison disease continues to have hyperkalemia despite receiving adequate replacement doses of hydrocortisone (cortisol). Which drug should be added to the treatment regimen to reduce serum potassium levels?

- (A) dexamethasone
- B) fludrocortisone
- (C) triamcinolone
- D) prednisone

- **5. Gradual tapering of a glucocorticoid is required for recovery of which of the following?**
- A)depressed release of insulin
- B)hematopoiesis in bone marrow
- C)normal osteoblast function
- D) hypothalamic pituitary adrenal axis


KEEP
CALM
IT'S
THE END OF
PRESENTATION