ADRENOCORTICOSTEROIDS

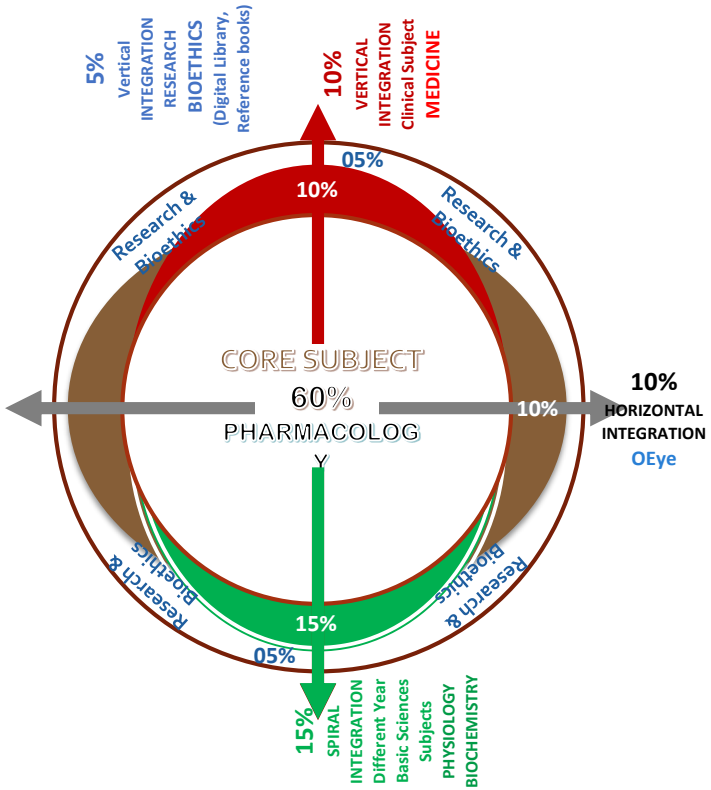
Sources:

- Bertram G. katzung Basic & Clinical Pharmacology 15th Edition-----page no. 728-744
- Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition….page no. 879-891

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



4rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Eye • Pathology
Vertical Integration – 10%	
Clinical Subjects	• Medicine • Surgery
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Research & Bioethics, Digital library – 05%	

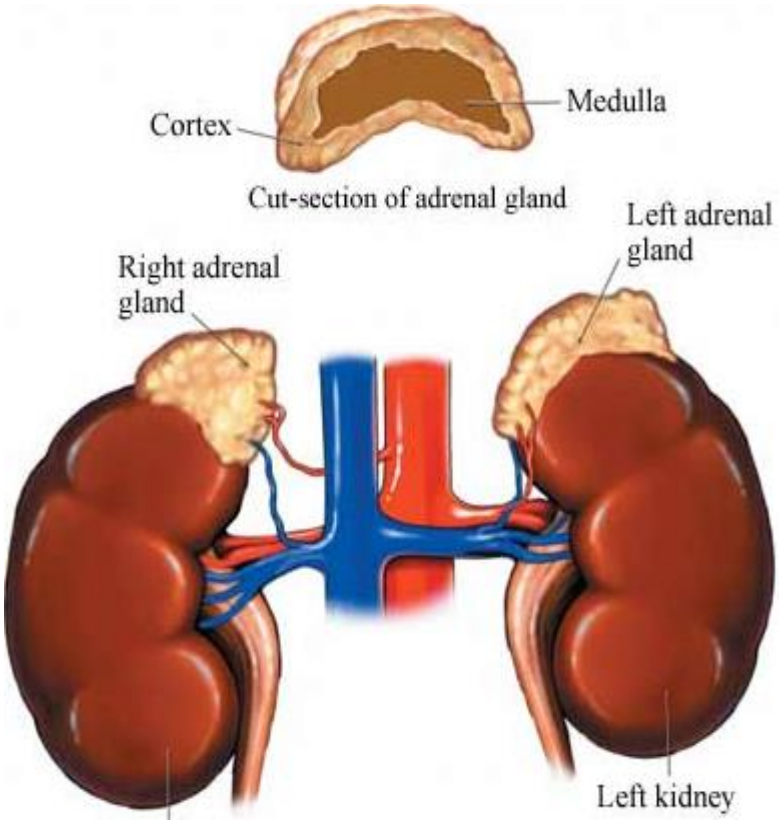
LEARNING OBJECTIVES

- At the end of the lecture, the students should be able to:

- ❑Recall anatomy and physiology related to adrenal glands and its function.
- ❑Classify glucocorticoids.
- ❑Discuss MOA and Pharmacological effects of steroids.
- ❑Rationalize the use of steroids in different clinical conditions.
- ❑Enumerate the adverse effects associated with their use.

SPIRAL INTEGERATION-ANATOMY

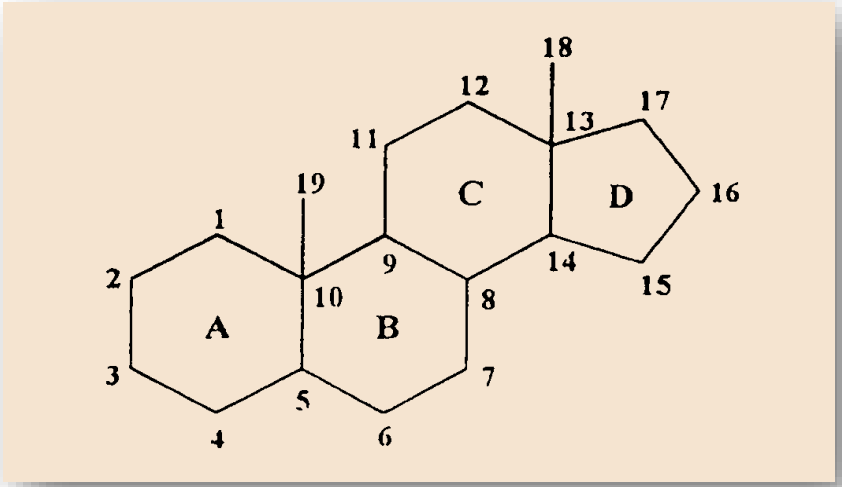
ADRENAL GLANDS



SPIRAL INTEGERATION- PHYSIOLOGY, BIOCHEMISTRY

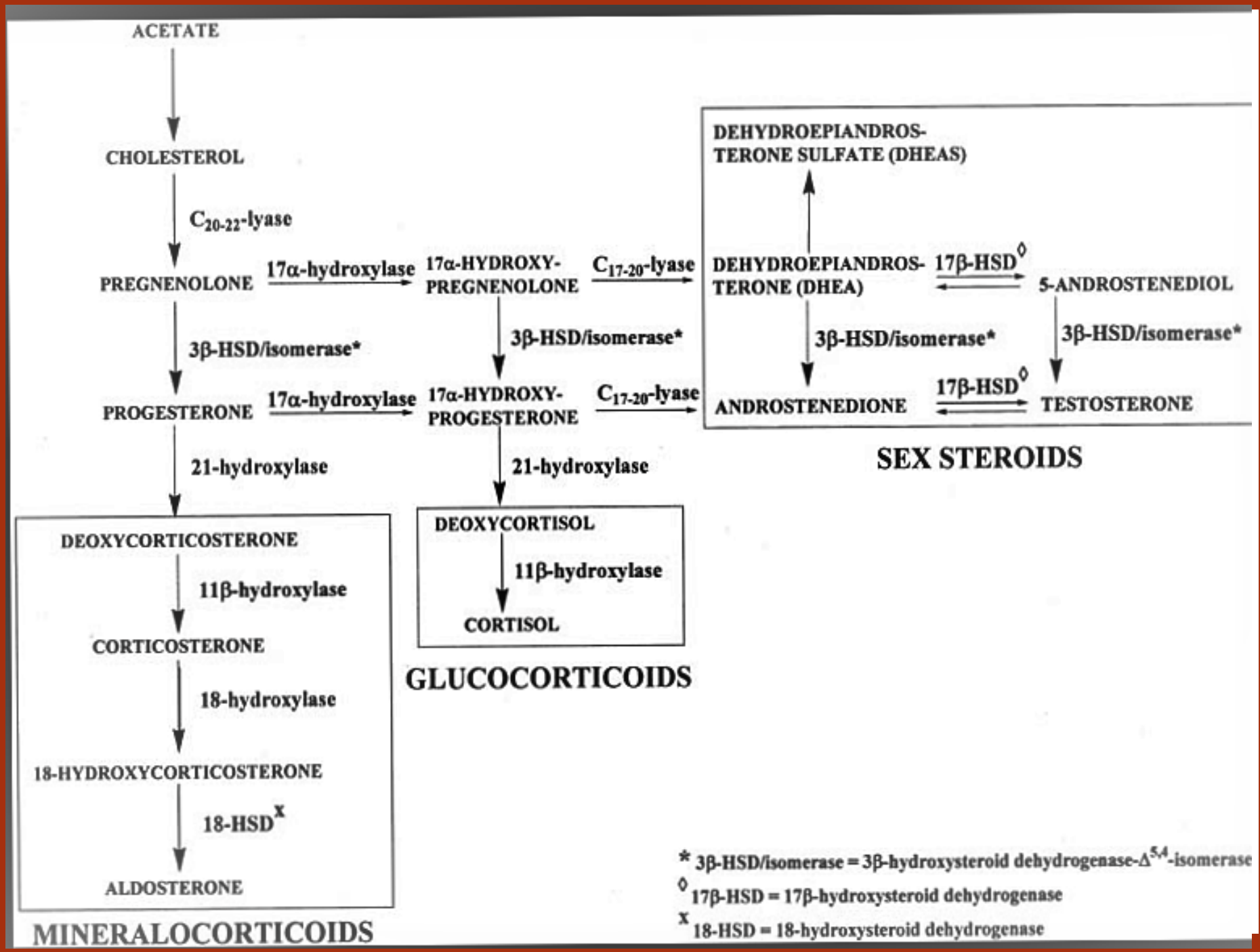
CORTICOSTEROIDS

- Corticosteroids are 21-C compounds having a ***cyclopentanoperhydro-phenanthrene*** (steroid) nucleus
- Synthesized in adrenal cortical cells from cholesterol



STEROID NUCLEUS

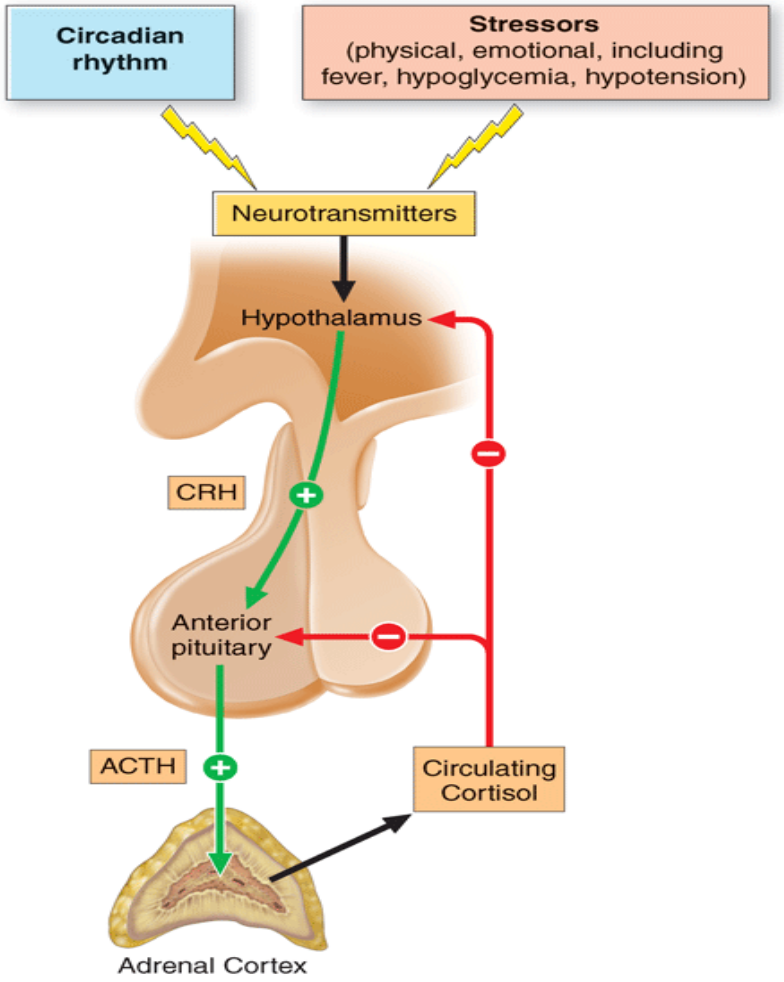
CYCLO-PENTANOPERHYDRO-PHENANTHRENE


ACETATE
CHOLESTEROL
C_{20-22}-lyase
PREGNENOLONE
17α-hydroxylase
17α-HYDROXY-PREGNENOLONE
C_{17-20}-lyase
3β-HSD/isomerase*
PROGESTERONE
17α-hydroxylase
17α-HYDROXY-PROGESTERONE
C_{17-20}-lyase
21-hydroxylase
21-hydroxylase
DEHYDROEPIANDROS-TERONE SULFATE (DHEAS)
DEHYDROEPIANDROS-TERONE (DHEA)
17β-HSD◊
5-ANDROSTENEDIOL
3β-HSD/isomerase*
3β-HSD/isomerase*
ANDROSTENEDIONE
17β-HSD◊
TESTOSTERONE
SEX STEROIDS
DEOXYCORTICOSTERONE
11β-hydroxylase
CORTICOSTERONE
18-hydroxylase
18-HYDROXYCORTICOSTERONE
18-HSDx
ALDOSTERONE
MINERALOCORTICOIDS
DEOXYCORTISOL
11β-hydroxylase
CORTISOL
GLUCOCORTICOIDS
* 3β-HSD/isomerase = 3β-hydroxysteroid dehydrogenase-$\Delta^{5,4}$-isomerase
◊ 17β-HSD = 17β-hydroxysteroid dehydrogenase
x 18-HSD = 18-hydroxysteroid dehydrogenase

REGULATION OF CORTICOSTEROID PRODUCTION

CNS regulate synthesis & secretion of GCs

- Autoregulation by negative feedback of circulating cortisol & exogenous glucocorticoids



CORTISOL (HYDROCORTISONE)

PHARMACOKINETICS

- Cortisol, synthesized from cholesterol
- 10–20 mg secreted daily, follows circadian rhythm, peak in early morning & after meals
- **90% bound to CBG (transcortin)**, 5–10% free or loosely bound to albumin
- **Half-life**---- 60–90 minutes
- **METABOLISM:** liver, metabolites conjugated to glucuronic acid or sulfate & then excreted by kidney

CORE SUBJECT

ADRENOCORTICOSTEROIDS

NATURAL

Glucocorticoids

Cortisol, Cortisone

Mineralocorticoids

Aldosterone, Corticosterone

Desoxycorticosterone acetate (DOCA)

SYNTHETIC

Glucocorticoids

Betamethasone, Dexamethasone, Triamcinolone

Prednisone, Prednisolone, Methylprednisolone

Mineralocorticoids

Fludrocortisone

GLUCOCORTICOIDS CLASSIFICATION ACCORDING TO DURATION OF ACTION

SHORT ACTING (t ½ 8-12 hrs)

Cortisol, Cortisone

INTERMEDIATE ACTING (t ½ 12-36 hrs)

Prednisone, Prednisolone, Methylprednisolone

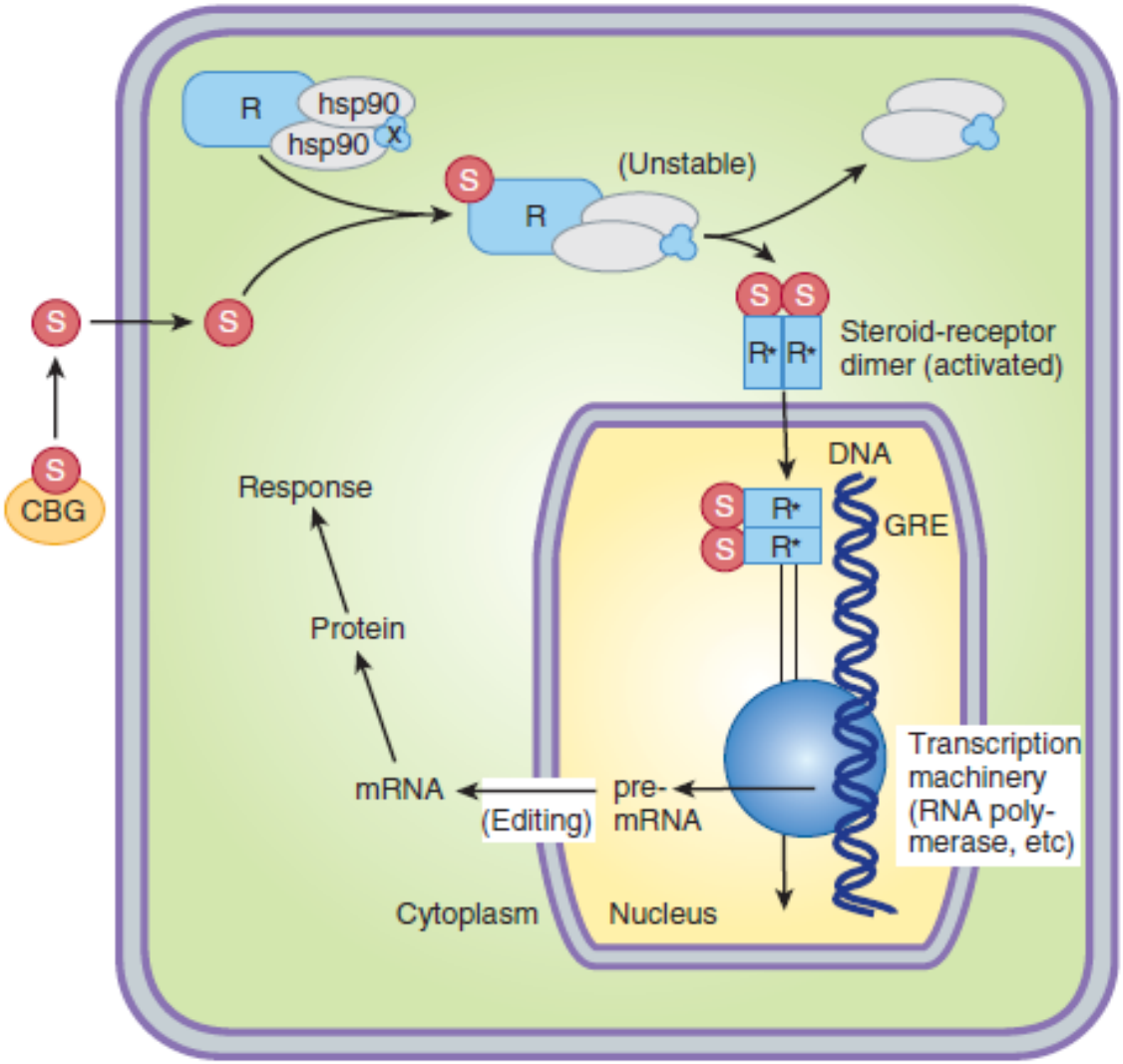
Triamcinolone

LONG ACTING (t ½ 36-72 hrs)

Paramethasone, Betamethasone

Dexamethasone

MECHANISM OF ACTION



PHARMACOLOGICAL ACTIONS OF CORTICOSTEROIDS

CARBOHYDRATE AND PROTEIN METABOLISM

- GCs maintain blood glucose levels during starvation thus protecting glucose dependent tissues (brain & heart) from starvation

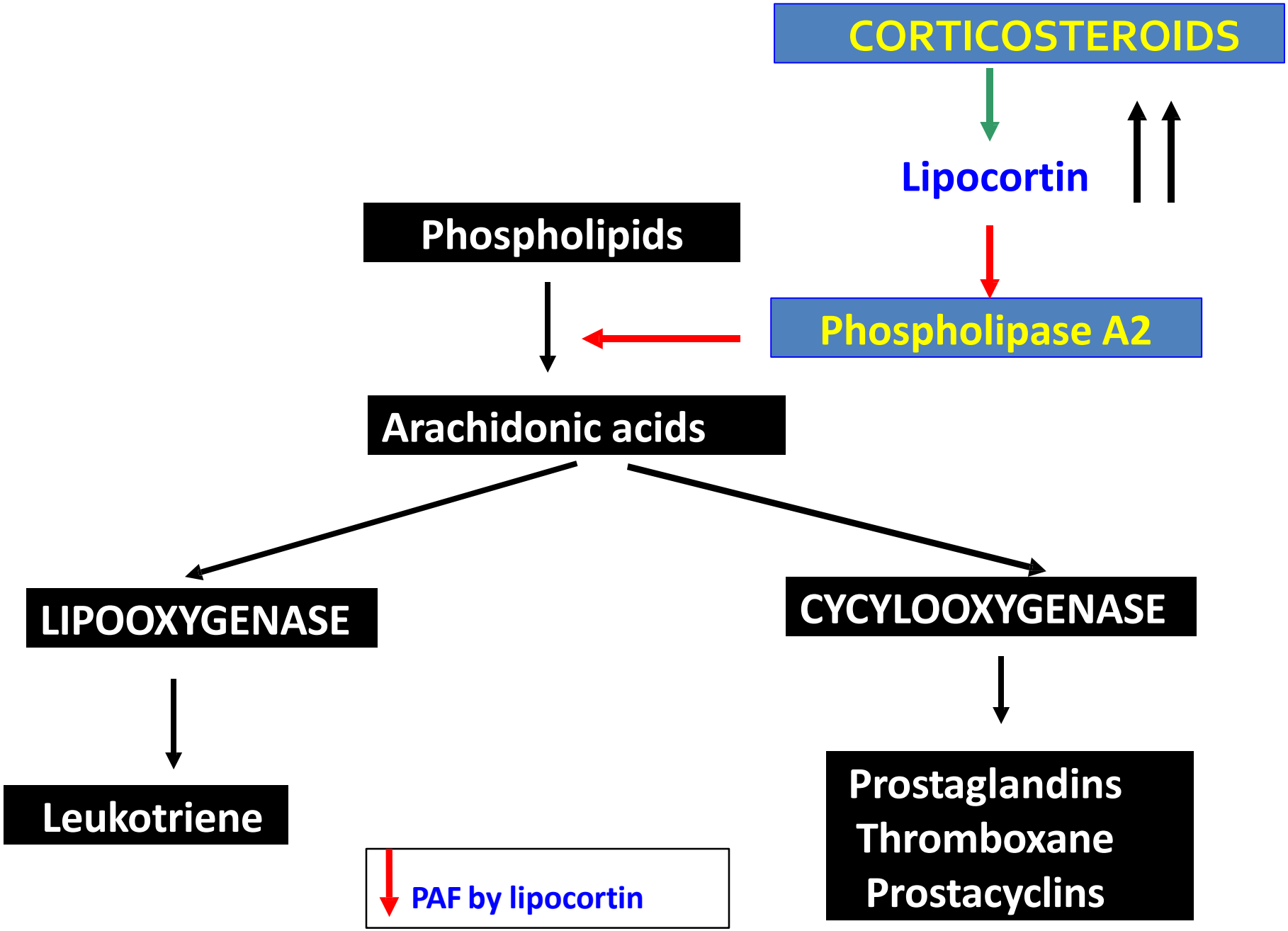
- ↑protein breakdown leads to decreased muscle mass, thinning of skin, negative nitrogen balance

PHARMACOLOGICAL ACTIONS OF CORTICOSTEROIDS

LIPID METABOLISM

- ***Promote lipolysis***

- ***Redistribution of body fat***


CORTICOSTEROIDS
Lipocortin
Phospholipids
Phospholipase A2
Arachidonic acids
LIPOOXYGENASE
CYCYLOOXYGENASE
Leukotriene
Prostaglandins
Thromboxane
Prostacyclins
PAF by lipocortin

PHARMACOLOGICAL ACTIONS OF CORTICOSTEROIDS

Lymphoid tissue and blood cells

- Increase number of RBCs & platelets, polycythemia occurs in Cushing's syndrome

CNS

- Have direct effect on CNS, affecting mood, behavior & brain excitability

PHARMACOLOGICAL ACTIONS OF CORTICOSTEROIDS

CVS

- **GCs directly stimulate cardiac output & potentiate responses of vascular smooth muscle to pressor effects of catecholamines other vasoconstrictor agents →HTN**

GASTROINTESTINAL EFFECTS

- Increase production of gastric acid & pepsin
- Suppress local immune response against Helicobacter pylori→ peptic ulcer

VERTICAL INTEGRATION-MEDICINE

THERAPEUTIC USES

1- REPLACEMENT THERAPY FOR *ADRENAL INSUFFICIENCY*

Acute adrenal insufficiency

Chronic adrenal insufficiency (Addison's disease)

THERAPEUTIC USES

2-Replacement therapy for congenital adrenal hyperplasia

- Most common defect is decrease or lack of ***21-hydroxylase activity,*** lead to a reduction in cortisol synthesis & compensatory increase in ACTH release

THERAPEUTIC USES

3- CUSHING'S SYNDROME—due to an ACTH secreting pituitary adenoma (Cushing's disease) or due to tumors of adrenal gland or ectopic production of ACTH by other tumors

- **Manifestations are those associated with chronic presence of excessive glucocorticoids**

4- DIAGNOSIS OF CUSHING'S SYNDROME

- ***Dexamethasone suppression test***

THERAPEUTIC USES

5- PRIMARY GENERALIZED GLUCOCORTICOID RESISTANCE (*CHROUSOS SYNDROME*)

- **Rare genetic disorder, due to mutations of *GC receptor gene* altering tissue sensitivity to glucocorticoids**
- **Increase activity of HPA axis to compensates for reduced sensitivity of peripheral tissues to glucocorticoids by hypersecretion of CRH & ACTH**

THERAPEUTIC USES

6- NON-ADRENAL USES

i. Inflammatory conditions of bones & joints --

ii. Renal diseases----

iii. Allergic diseases----

iv. Pulmonary diseases----

THERAPEUTIC USES

NON-ADRENAL USES

v. *Hematologic disorders---*

vi. *Thyroid diseases---*

vii. *Cerebral edema, Multiple sclerosis*

viii. *Prevention & treatment of organ transplant rejection*

ADVERSE EFFECTS OF CORTICOSTEROIDS

Iatrogenic Cushing's syndrome, characteristic appearance due to ***redistribution of body fat*** , ↑fat in back of neck("buffalo hump"),face(" moon facies") & supraclavicular area with loss of fat in extremities

ADVERSE EFFECTS OF CORTICOSTEROIDS

Metabolic

- Hyperglycemia with glycosuria & Adrenal Diabetes
- Protein wasting
- Obesity

Immune Responses

- ↑ susceptibility of bacterial & mycotic infections
- ↑ risk for reactivation of latent tuberculosis
- Impaired wound healing

GIT

- Acute peptic ulcers
- Acute pancreatitis

ADVERSE EFFECTS OF CORTICOSTEROIDS

Central nervous system

- Insomnia, hypomania, depression, nervousness & psychosis
- Benign intracranial hypertension

Musculoskeletal

- Myopathy & muscle wasting
- Thinning of skin, with striae & bruising
- Growth retardation in children
- ***Osteoporosis***
- ***Avascular or aseptic necrosis*** ,femoral head affected most frequently, but may also affect humeral head & distal femur

ADVERSE EFFECTS OF CORTICOSTEROIDS

Ocular

- Posterior subcapsular cataracts
- Increased intraocular pressure & glaucoma

- ***Suppression of HPA axis*** → ***ADRENAL SUPPRESSION*** administered for more than 2 weeks

STEROID WITHDRWAL

- If corticosteroids are administered for more than 2 wks, adrenal suppression occur because exogenous GCs suppress hypothalamic CRH & pituitary ACTH
- With prolonged suppression, adrenal glands atrophy & take several months to recover full function after discontinuation of exogenous GCs, It may take 2–12 months for HPA-axis to function normally
- . If treatment extends to months, additional therapy should be given at times of minor stress or severe stress
- If GCs dosage is to be reduced, it should be tapered slowly, rapid dose reduction cause, **flare-up** of **underlying disease** for which steroids were prescribed

CONTRAINDICATIONS

- Peptic ulcer
- Heart disease or hypertension with heart failure
- Infectious illnesses such as varicella & tuberculosis
- Psychoses
- Diabetes
- Osteoporosis
- Glaucoma
- Pregnancy(Risk of fetal defects)

RESEARCH

Pivonello, R., Ferrigno, R., De Martino, M.C., Simeoli, C., Di Paola, N., Pivonello, C., Barba, L., Negri, M., De Angelis, C. and Colao, A., 2020. Medical treatment of Cushing's disease: an overview of the current and recent clinical trials. *Frontiers in Endocrinology*, *11*, p.648.

BIOETHICS

Shakeel, Sadia, Shagufta Nesar, Wajiha Iffat, Hina Rehman, Samreen Aziz, Tayyaba Mumtaz, Hazrina Hadi, and Shazia Jamshed. 2021. "Pharmacists' Insights and Behaviors in Preventing the Misuse of Topical Corticosteroids in Pakistan: A Mixed-Method Study" *Cosmetics* 8, no. 3: 72

ARTIFICIAL INTELLIGENCE

- Jiang L, Li M, Jiang H, Tao L, Yang W, Yuan H, He B. Development of an Artificial Intelligence Model for Analyzing the Relationship between Imaging Features and Glucocorticoid Sensitivity in Idiopathic Interstitial Pneumonia. *International Journal of Environmental Research and Public Health*. 2022; 19(20):13099. https://doi.org/10.3390/ijerph192013099

- Nguyen, L.S., Prifti, E., Ichou, F. *et al.* Effect of congenital adrenal hyperplasia treated by glucocorticoids on plasma metabolome: a machine-learning-based analysis. *Sci Rep* **10**, 8859 (2020). https://doi.org/10.1038/s41598-020-65897-y

END OF LECTURE ASSESSMENT

1. Which of the following synthetic glucocorticoids also has some mineralocorticoid activity?

a. Betamethasone

b. Dexamethasone

c. Paramethasone

d. Prednisone

e. Triamcinolone

- Which of the following may be used for treatment of Cushing's syndrome?

a. Dexamethasone
b. Fludrocirtisone
c. Ketoconaole
d. Prednisone
e. Spirolactone

- The drug used to treat Cushing's syndrome and may cause hepatotoxicity is

a. Acetaminophen
b. Aspirin
c. Indomethacin
d. Ketoconazole
e. Metyrapone

- The drug given along with epinephrine for anaphylactic shock is

a. Acetaminophen
b. Aspirin
c. Fludrocortisone
d. Hydrocortisone
e. Spironolactone

- The drug used for osteoporosis caused by high dose of glucocorticoids

a. Alendronate
b. Anastrozole
c. Ethinyl estradiol
d. Omeprazole
e. Oxandrolone