Pharmacology of Corticosteroids

By

Mohammed M. Alanazi, B.Pharm, Ph.D

Assistant Professor

Department of Pharmacology and Toxicology

College of Pharmacy, KSU

momalanazi@ksu.edu.sa

Office# 1A29 – College of Dentistry

Slides are adopted and modified from **Dr. Alia Alshanawani**

Objectives

- By the end of this lecture, the student will be able to Know Corticosteroids: glucocorticoids (GCs) and mineralocorticoids (MCs) from different perspectives:

  - Their synthesis
  - Their Mechanism of actions
  - Their Metabolic, catabolic, anti-inflammatory and immunosuppressive effects
  - Some examples of GCs and MCs
    - Some of their clinical uses
    - Toxicity
    - GCs and MCs antagonists

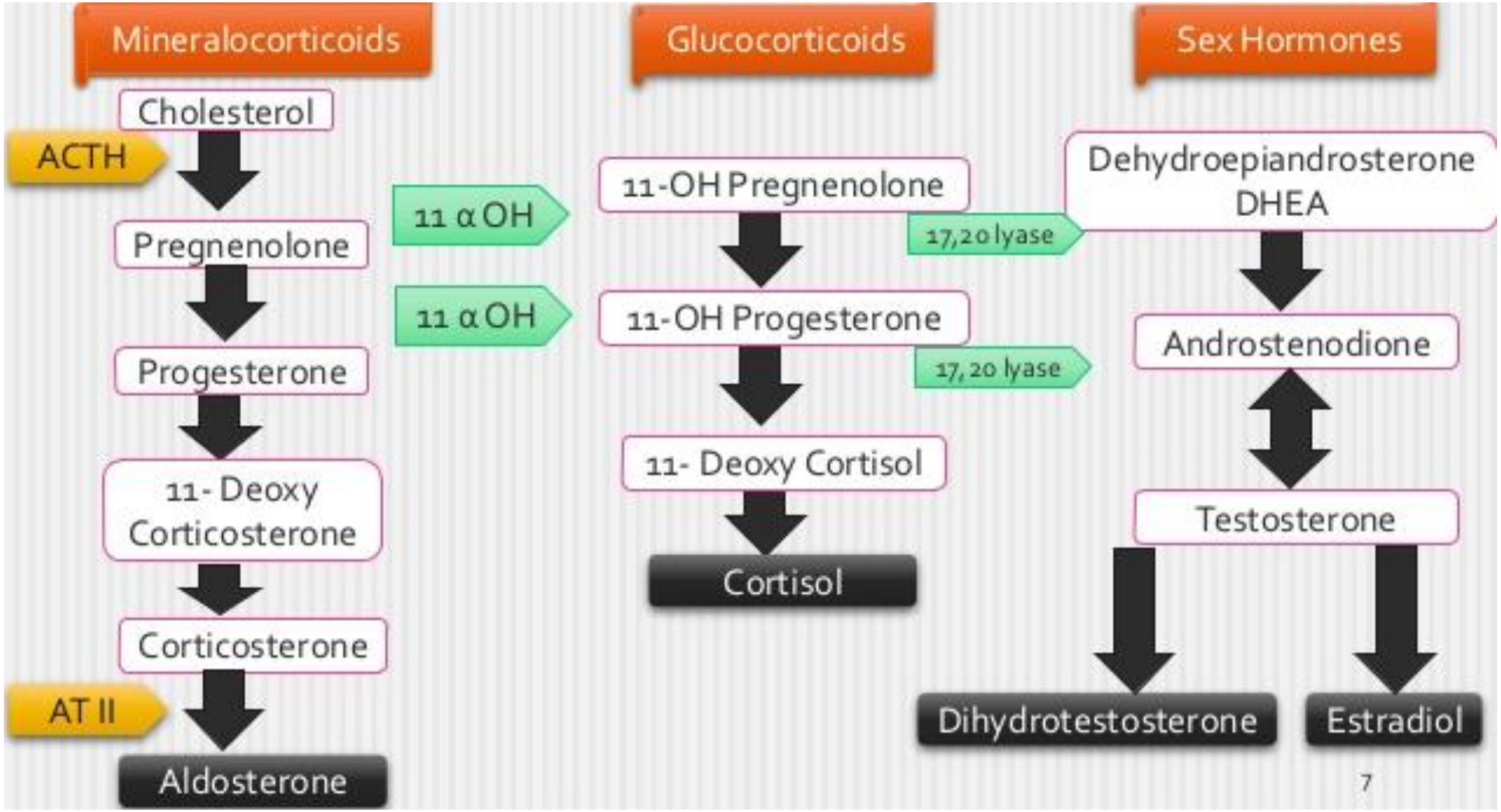
Introduction

- The **Corticosteroids** are steroid hormones produced by the adrenal cortex.

- **They consist of two major groups:**

1. Glucocorticoids [Major cortisol (Hydrocortisone)]
2. Mineralocorticoids (most important Aldosterone)

Biosynthesis of Adrenal Hormones



GCs and MCs Effects:

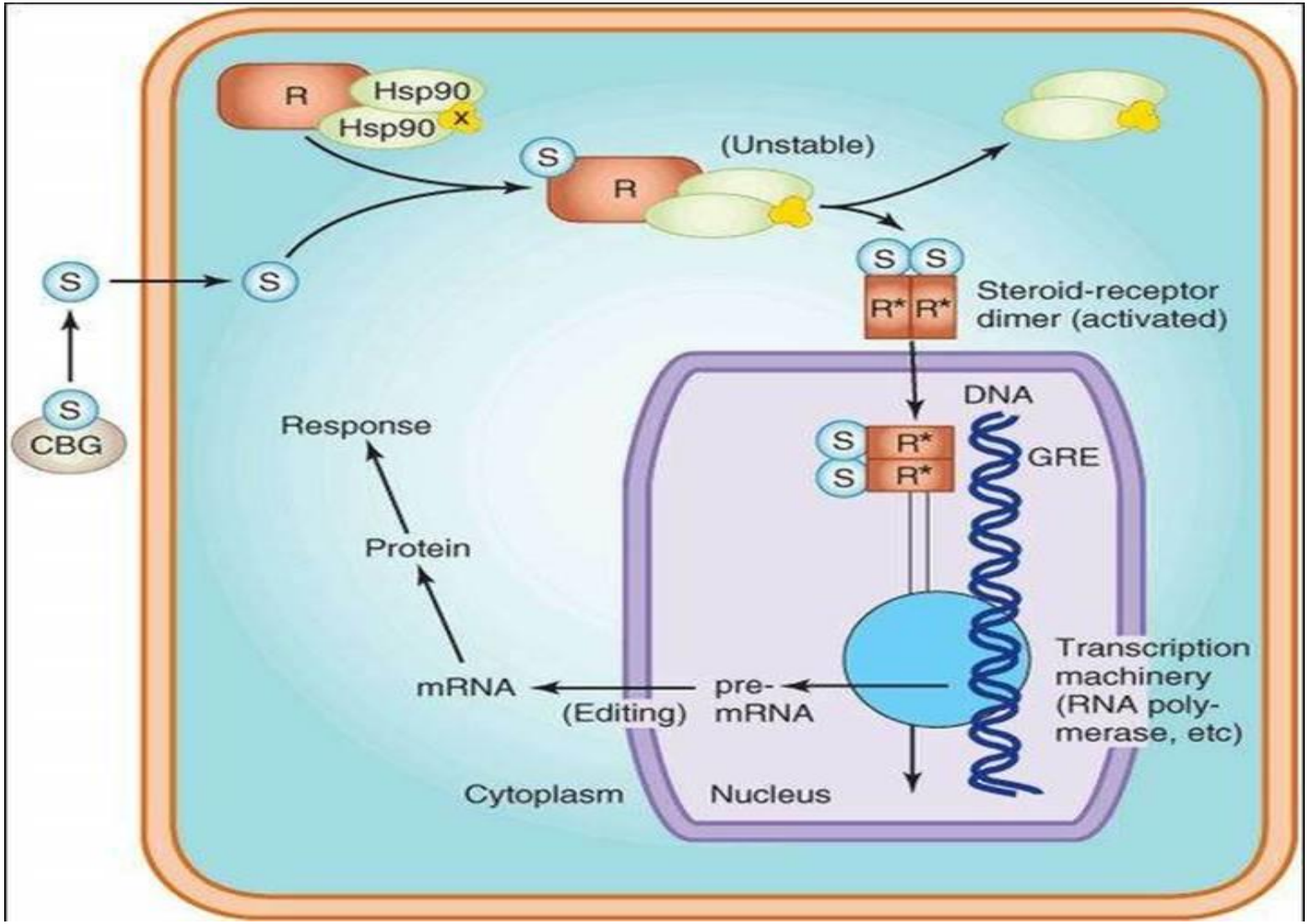
- **Glucocorticoids:**

They have important effects on intermediary metabolism, catabolism, immune responses, growth and inflammation.

- **Mineralocorticoids:**

They have salt-retaining activity which regulate sodium & potassium reabsorption in the collecting tubules of the kidney.

GCs Mechanism of Action



GCs Mechanism of Action

- Corticosteroid is present in the blood bound to the **corticosteroid binding globulin** (CBG) & enters the cell as the free molecule.

- The intracellular receptor (R) is bound to the stabilizing proteins, including heat shock protein 90 (Hsp90) & several others (X). When the complex binds a molecule of steroid, the Hsp90 & associated molecules are released.

GCs Mechanism of Action

- The Steroid– R complex enters the nucleus as a dimer, binds to the **glucocorticoid response element** (GRE) on the gene & regulates gene transcription by RNA polymerase II & associated transcription factors.

- The resulting mRNA is edited & exported to the cytoplasm for the production of protein that brings about the final hormone response.

GCs Metabolic effects

- **<u>Glucocorticoids stimulate gluconeogenesis, as a result</u>:**
    - Blood glucose rises
    - Insulin secretion is stimulated
    - Stimulate lipolysis & lipogenesis (due to increased insulin)

- With a net increase of fat deposition in certain areas e.g, the face (moon faces) and shoulder & back (buffalo hump).
- These effects occur when the patient is treated with 100 mg of hydrocortisone or > for longer than 2 weeks.

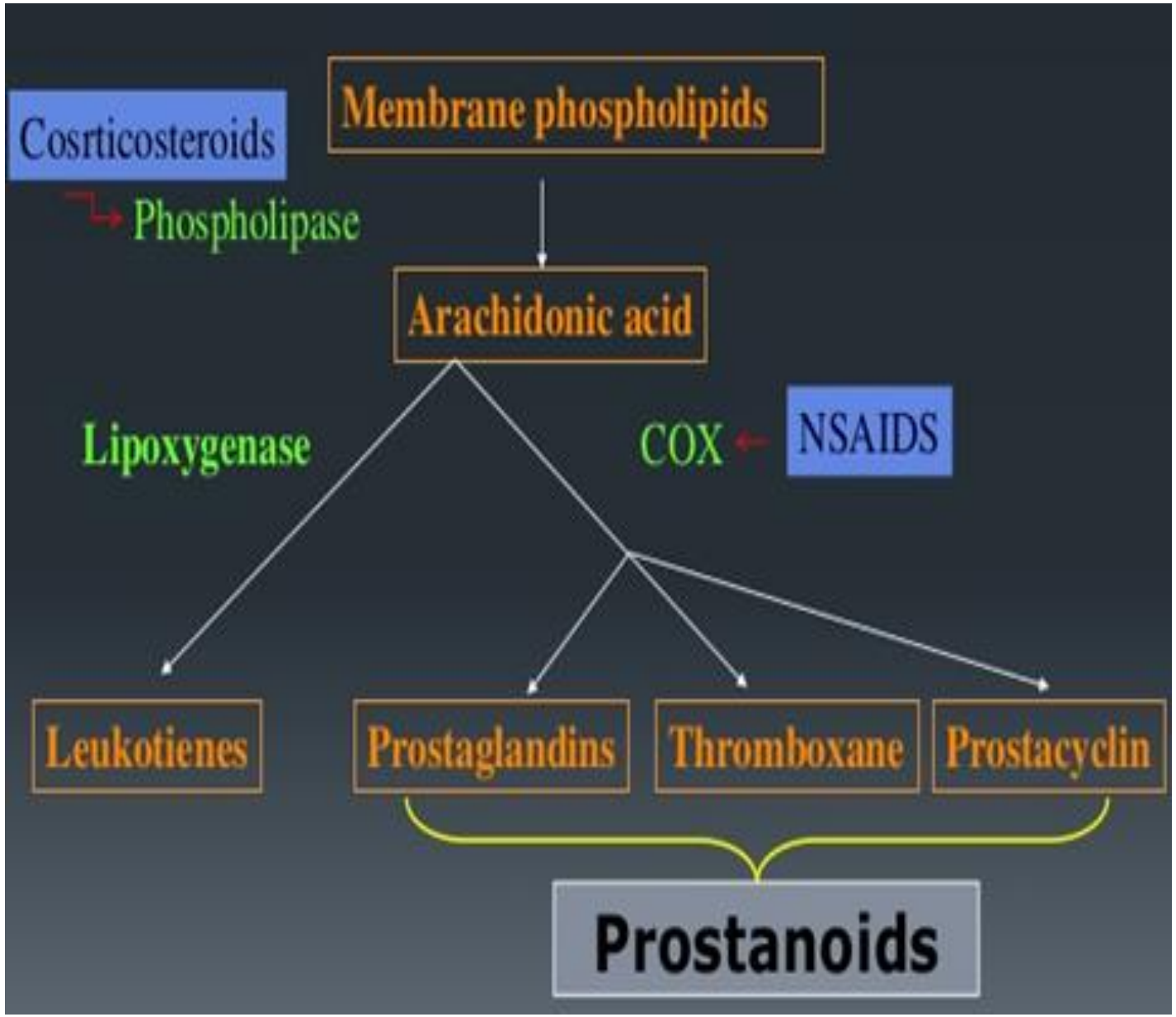
GCs Catabolic effects

- Glucocorticoids cause muscle **protein** catabolism (muscle mass)
- Lymphoid & connective tissue **fat** & skin undergo wasting
- Catabolic effects on **bone** lead to osteoporosis
- In **children, growth** is inhibited.

GCs Anti–inflammatory effects

- Glucocorticoids have important inhibitory effects on the distribution, function & migration of **leukocytes**
- Suppressive effect on the inflammatory **cytokines** & **chemokines**

- These drugs increase neutrophils & decrease **lymphocytes**, **eosinophils**, **basophils** & **monocytes**
- MOA: Inhibit phospholipase A2 & **Prostaglandins** synthesis.


Cosrticosteroids
Membrane phospholipids
Phospholipase
Arachidonic acid
Lipoxygenase
COX
NSAIDS
Leukotienes
Prostaglandins
Thromboxane
Prostacyclin
Prostanoids

GCs Immunosuppressive effects

- Glucocorticoids **inhibit** cell-mediated immunologic functions, especially dependent on **lymphocytes** & decrease **interleukins** secretion.

- Glucocorticoids do not interfere with the development of normal acquired immunity but delay rejection reactions in patients with organ transplants.

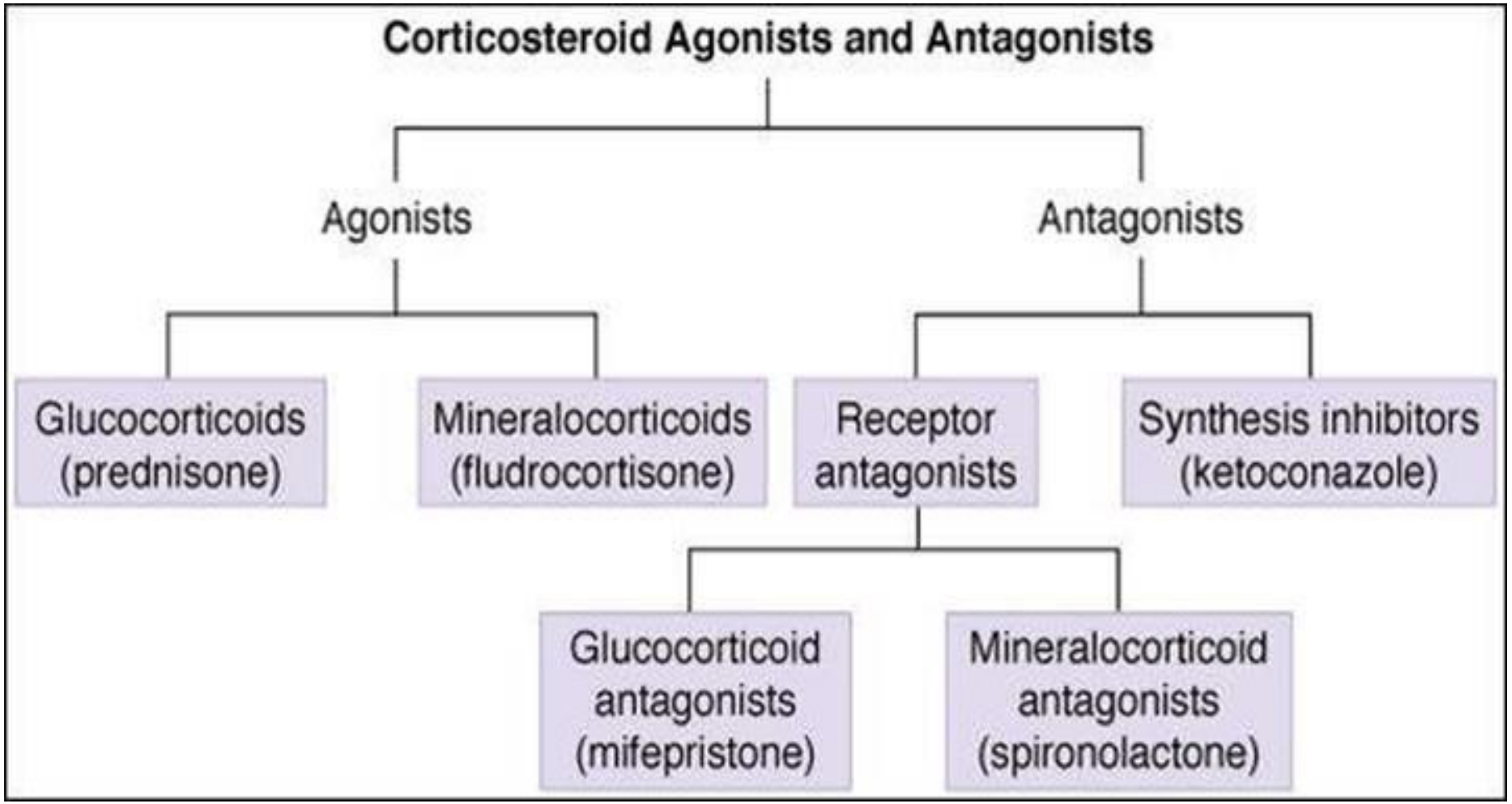
GCs Other effects

- Glucocorticoids such as **cortisol** are required for normal **renal excretion of water** loads.

- **CNS**: When given in large doses these drugs may cause profound behavioral changes (first insomnia & euphoria then depression).

- **GIT**: Large doses also stimulate **gastric acid secretion** & decrease resistance to ulcer formation.

Examples for Corticosteroids: Agonists vs. Antagonists



Examples for Glucocorticoids

- **Cortisol (hydrocortisone)**
- The major natural glucocorticoid
- The physiologic secretion of cortisol is regulated by adrenocorticotropin hormone (ACTH) & secretion rate varies during the day (circadian rhythm), peaks in the early morning & declines about midnight.

Cortisol Pharmacokinetics

- Given **orally**, cortisol is well absorbed from GIT
- Cortisol in the plasma is 95% bound to **CBG**

- It is metabolized by the **liver** & has **short** duration of action compared with the synthetic congeners
- It diffuses **poorly** across normal skin & mucous membranes

- The cortisol molecule also has a small but significant mineralocorticoid effect. This is an important cause of **hypertension** in patients with cortisol secreting **adrenal** tumor or a **pituitary** ACTH secreting tumor (Cushing's syndrome).

Examples for Glucocorticoids

- **Synthetic Glucocorticoids**

Large number are available for use:

Prednisone & its active metabolite prednisolone

Dexamethasone

Beclomethasone

Budesonide

Synthetic Glucocorticoids

- **Their properties (compared with cortisol) include:**

  - Longer half life & duration of action
  - Reduce salt retaining effect
  - Better penetration of lipid barriers for topical activity.

Agent	Activity[1]			Equivalent Oral Dose (mg)	Forms Available
	Anti-Inflammatory	*Topical*	*Salt-Retaining*		
Short- to medium-acting glucocorticoids					
Hydrocortisone (cortisol)	1	1	1	20	Oral, injectable, topical
Cortisone	0.8	0	0.8	25	Oral
Prednisone	4	0	0.3	5	Oral
Prednisolone	5	4	0.3	5	Oral, injectable
Methylprednisolone	5	5	0.25	4	Oral, injectable
Meprednisone[2]	5		0	4	Oral, injectable
Intermediate-acting glucocorticoids					
Triamcinolone	5	5[3]	0	4	Oral, injectable, topical
Paramethasone[2]	10		0	2	Oral, injectable
Fluprednisolone[2]	15	7	0	1.5	Oral
Long-acting glucocorticoids					
Betamethasone	25–40	10	0	0.6	Oral, injectable, topical
Dexamethasone	30	10	0	0.75	Oral, injectable, topical
Mineralocorticoids					
Fludrocortisone	10	0	250	2	Oral
Desoxycorticosterone acetate[2]	0	0	20		Injectable, pellets

[1]Potency relative to hydrocortisone.

[2]Outside USA.

[3]Triamcinolone acetonide: Up to 100.

Synthetic Glucocorticoids

- **Beclomethasone & budesonide** have been developed for use in **asthma** & other conditions in which good surface activity on **mucous membrane or skin** is needed & systemic effects are to be avoided.

- These drugs **rapidly** penetrate the **airway mucosa** but have very short half lives after they enter the blood, so that systemic effects & toxicity are greatly **reduced**.

Clinical uses of corticosteroids

❖**Adrenal disorders:**

- Addison’s disease (**chronic** adrenal cortical insufficiency)
- **Acute** adrenal insufficiency associated with life threatening shock, infections or trauma
- Congenital adrenal hyperplasia (in which synthesis of **abnormal forms** of corticosteroids are stimulated by ACTH).

Clinical uses of corticosteroids

❖**Non-adrenal disorders:**

- Allergic reactions (e.g. bronchial asthma, angioneurotic edema, drug reactions, urticaria, allergic rhinitis)
- Collagen vascular disorder (e.g; rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, polymyositis, mixed connective tissue syndrome)
- Organ transplants (prevention & treatment of rejection – immunosuppression).

Clinical uses of corticosteroids

- **Non-adrenal disorders:**

- GI disorders such as inflammatory bowel disease
- Hematologic disorders (leukemia, multiple myeloma, acquired hemolytic anemia, acute allergic purpura)
- Infections (acute respiratory distress syndrome, sepsis)
- Neurologic disorders (to minimize cerebral edema after brain surgery, multiple sclerosis).

Clinical uses of corticosteroids

❖**Non-adrenal disorders:**

- Pulmonary diseases (e.g.; aspiration pneumonia, bronchial asthma, sarcoidosis).
- Thyroid diseases (malignant exophthalmos, subacute thyroiditis)
- Renal disorders (nephrotic syndrome)
- Miscellaneous (hypercalcemia, mountain sickness).

Corticosteroids Toxicity (Adverse effects)

- Cushing's syndrome (iatrogenic, by higher doses > than 100 mg hydrocortisone daily for > than 2 weeks characterized by moon shape face & buffalo hump)
- Increased growth of fine hair on face, thighs & trunk. Myopathy, muscle wasting, thinning of skin, Diabetes Mellitus
- Osteoporosis & aseptic necrosis of the hip
- Wound healing is impaired

Corticosteroids Toxicity (Adverse effects)

- Peptic ulcer
- Acute psychosis, depression
- Subcapsular cataracts
- Growth suppression
- Hypertension
- Adrenal suppression.

Methods for minimizing these toxicities include

- Local application (e.g, aerosol for asthma)
- Alternate day therapy (to reduce pituitary suppression)
- Tapering the dose soon after achieving a therapeutic response
- To avoid adrenal insufficiency in patients who have had long term therapy, **additional stress doses** may need to be given during serious illness, or before major surgery.

Examples for Mineralocorticoids:

- **Aldosterone:**
- The major **natural** mineralocorticoid in human.
- Aldosterone is the main salt-retaining hormone, promotes Na reabsorption, K excretion, in the distal convoluted tubule & thus it is very important in the regulation of blood volume & blood pressure. Its secretion is regulated by ACTH & by the renin-angiotensin system.
- Aldosterone has short half life & little glucocorticoid activity.

Examples for Mineralocorticoids:

- **Aldosterone Mechanism of action:**
  - Same as that of glucocorticoids.

- **Fludrocortisone** is favored for replacement therapy after adrenalectomy & in other conditions in which mineralocorticoid therapy is needed.

Examples for GCs Antagonists:

- **Receptor Antagonists:**

- **Spironolactone** (mineralocorticoid antagonist & K-sparing diuretic)
  - antagonists of aldosterone at its receptor, used in the treatment of primary aldosteronism (**Conn's syndrome).**

- **Mifepristone:**
  - A competitive inhibitor of glucocorticoid receptors & useful in the treatment of Cushing's syndrome.

Examples for GCs Antagonists:

Synthesis inhibitors:

- **Ketoconazole (anti fungal)**
- **Clinical uses:**
- **Adrenal cancer**, when surgical therapy is impractical or unsuccessful because of metastasis.

Examples for GCs Antagonists:

- **Mechanism of Action of Ketoconazole:**
- It inhibits the cytochrome p450 enzymes necessary for the synthesis of all steroids & is used in a no. of conditions in which reduced steroid level are desirable such as:
    1. Adrenal carcinoma
    2. Hirsutism
    3. Breast cancer
    4. Prostate cancer.

Questions ???