Pharmacology of Corticosteroids

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ILOs

By the end of this lecture you will be able to:

- Revise the synthesis of steroids
- Mechanism of action
- Pharmacokinetics of cortisol, pharmacodynamic actions and therapeutic uses
- Adverse reaction
- Steroids agonists and antagonists and their therapeutic applications.

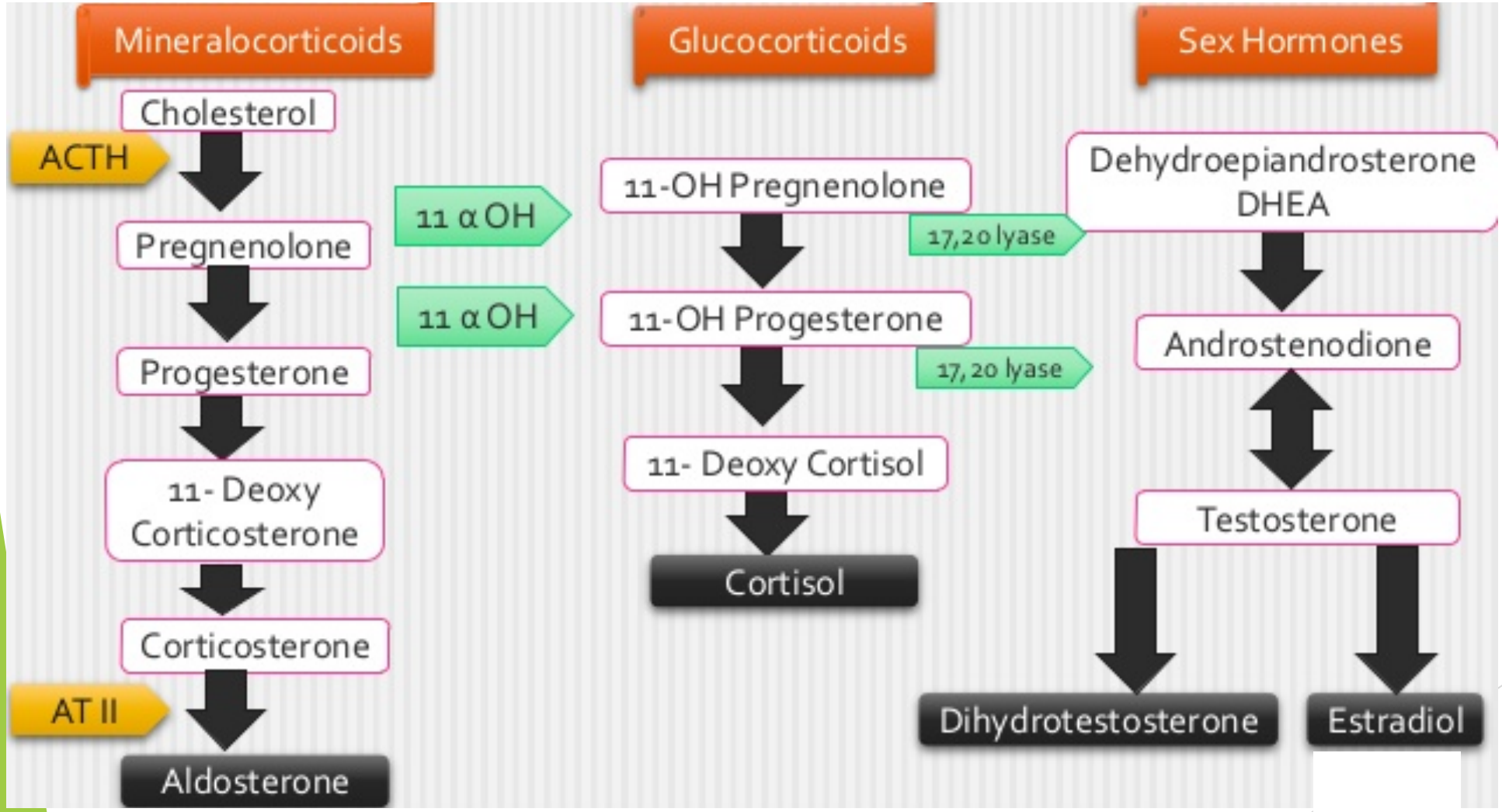
The **Corticosteroids** are steroid hormones produced by the adrenal cortex.

They consist of two major groups:

1. **Glucocorticoids [Major cortisol (Hydrocortisone)]**

2. **Mineralocorticoids (most important Aldosterone)**

Biosynthesis of adrenal hormones



1. **Glucocorticoids:**

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

2. **Mineralocorticoids:**

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

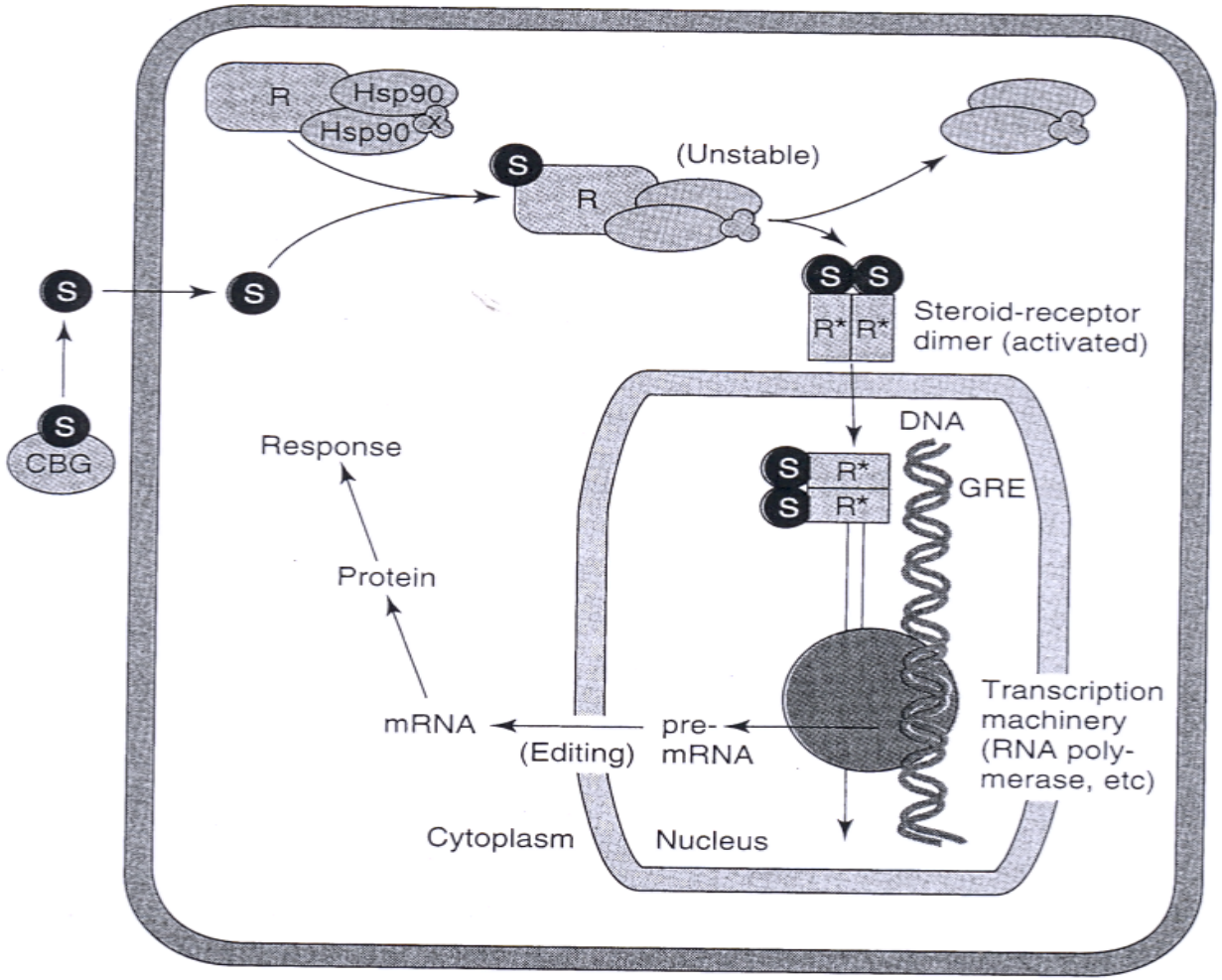


Figure 39–1. Mechanism of glucocorticoid action. This figure models the interaction of a steroid (S; eg, cortisol), with its receptor (R) and the subsequent events in a target cell. The steroid is present in the blood bound to the corticosteroid-binding globulin (CBG) but enters the cell as the free 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 by RNA polymerase II and associated transcription factors. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology,* 10th ed. McGraw-Hill, 2007.)

Pharmacodynamics
A. 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.

- 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.

B. **Metabolic effects:**

- **Glucocorticoids stimulate gluconeogenesis, as a result:**

  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) & shoulder & back (buffalo hump).

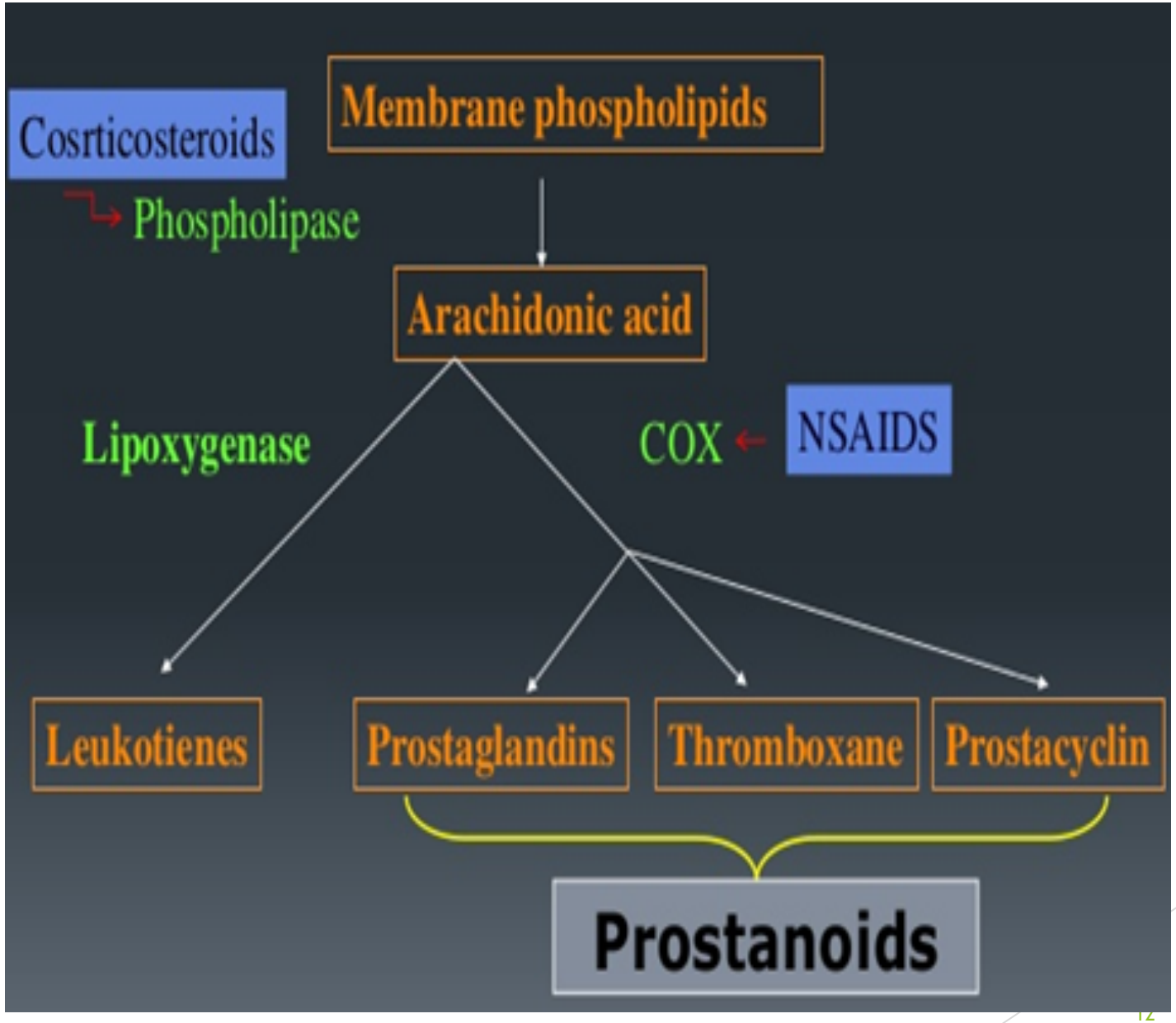
These effects occur when the patient is treated with 100 mg of hydrocortisone or > for longer than 2 weeks.

C. 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.

D. 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**
- Inhibit phospholipase A2 & **Prostaglandins** synthesis.

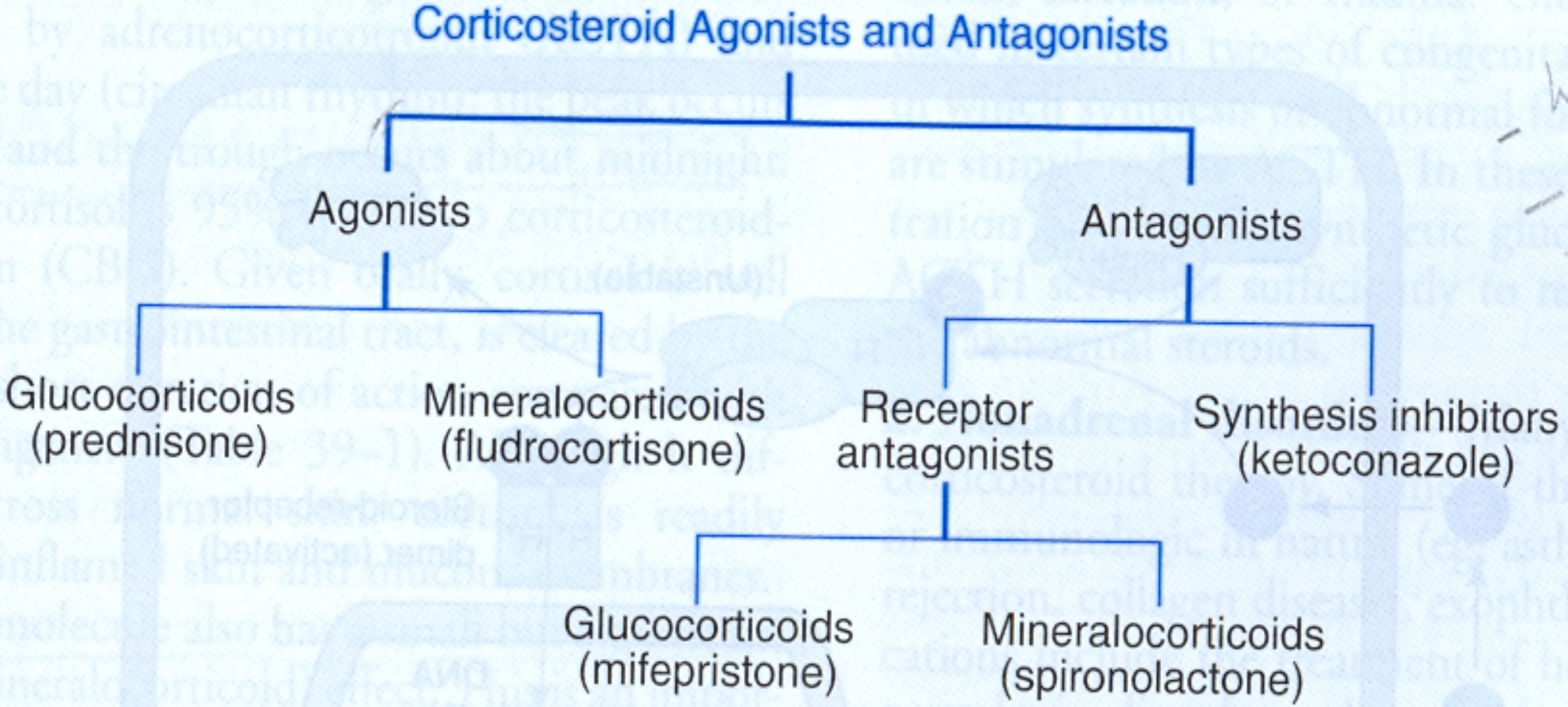

Membrane phospholipids
Cosrticosteroids
Phospholipase
Arachidonic acid
Lipoxygenase
COX
NSAIDS
Leukotienes
Prostaglandins
Thromboxane
Prostacyclin
Prostanoids

E. 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.

F. 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.


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

Important Glucocorticoids:

1- 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.

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).

2. Synthetic Glucocorticoids

Large number are available for use:

Prednisone & its active metabolite prednisolone

Dexamethasone

Beclomethasone

Budesonide

Their properties (compared with cortisol) include:

longer half life & duration of action

reduce salt retaining effect

better penetration of lipid barriers for topical activity.

TABLE 39–1 Some commonly used natural and synthetic corticosteroids for general use.

Agent	Activity[1]			Equivalent Oral Dose (mg)	Forms Availabl
	Anti-Inflammatory	*Topical*	*Salt-Retaining*		
Short- to medium-acting glucocorticoids					
Hydrocortisone (cortisol)	1	1	1	20	Oral, injectable,
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,
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,
Dexamethasone	30	10	0	0.75	Oral, injectable,
Mineralocorticoids					
Fludrocortisone	10	0	250	2	Oral
Desoxycorticosterone acetate[2]	0	0	20		Injectable, pelle

- **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

- **A. Adrenal disorders:**

1. Addison's disease (**chronic** adrenal cortical insufficiency)

2. **Acute** adrenal insufficiency associated with life threatening shock, infections or trauma

3. Congenital adrenal hyperplasia (in which synthesis of **abnormal forms** of corticosteroids are stimulated by ACTH).

B. Non-adrenal disorders:

1. Allergic reactions (e.g. bronchial asthma, angioneurotic edema, drug reactions, urticaria, allergic rhinitis)

2. Collagen vascular disorder (e.g; rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, polymyositis, mixed connective tissue syndrome)

3. Organ transplants (prevention & treatment of rejection – immunosuppression).

4. GI disorders such as inflammatory bowel disease

5. Hematologic disorders (leukemia, multiple myeloma, acquired hemolytic anemia, acute allergic purpura)

6. Infections (acute respiratory distress syndrome, sepsis)

7. Neurologic disorders (to minimize cerebral edema after brain surgery, multiple sclerosis).

8. Pulmonary diseases (e.g.; aspiration pneumonia, bronchial asthma, sarcoidosis).

9. Thyroid diseases (malignant exophthalmos, subacute thyroiditis)

10. Renal disorders (nephrotic syndrome)

11. Miscellaneous (hypercalcaemia, mountain sickness).

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
- 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.

Mineralocorticoids:

A. 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.

Mechanism of action:

Same as that of glucocorticoids.

Fludrocortisone is favored for <u>replacement therapy</u> after adrenalectomy & in other conditions in which mineralocorticoid therapy is needed.

Corticosteroid Antagonists:

A. 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.

B. Synthesis inhibitors:

- **Ketoconazole (anti fungal)**

Clinical uses:

Adrenal cancer, when surgical therapy is impractical or unsuccessful because of metastasis.

Ketoconazole :

Mechanism of Action:

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.