Faculty of Pharmacy
1st Semester (2020-2021)
Pharmaceutical Chemistry II
Topic 5

STEROID HORMONES AND THERAPEUTICALLY RELATED COMPOUNDS

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Ph.D. in Drug Control

Endocrine System

- The endocrine system refers to the collection of ductless glands of human body that secrete hormones directly into the spaces surrounding their cells (interstitial fluid) and blood to be carried towards distant target organs e.g. pituitary gland
- The endocrine system's effects are slow to initiate, and prolonged in their response, lasting from a few hours up to weeks.

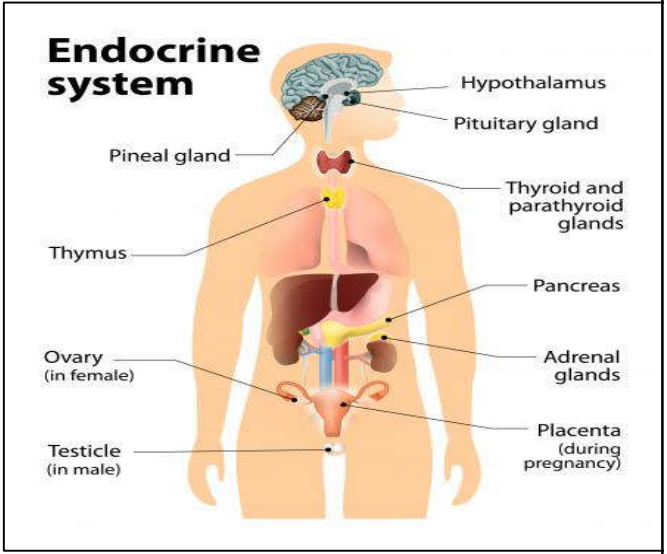
Hormones

- They are chemical messengers that bind to receptors on target cells, which leads to some change in that cells physiologic state.
- They affect the cell that made them or a cell distant to their origin.
- These messengers control the most major body functions by interacting with target cells which bear specific receptors for that particular hormone.

Classification of hormones

According to secreting organ:

1. **Hypothalamus**
2. **Pituitary gland**
   - **Anterior pituitary lobe**
   - **Posterior pituitary lobe**
3. **Thyroid**
4. **Digestive system: Pancreas**
5. **Adrenal glands**
6. **Reproductive: Testes & Ovaries**



Classification of hormones

According to chemical structure:

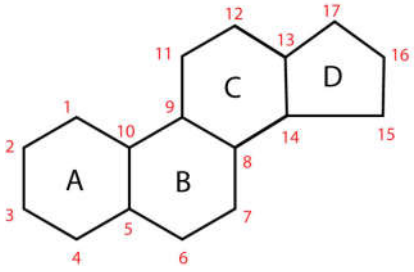
1. **Steroid hormones** are fat-soluble molecules made from cholesterol e.g. estrogens and androgens.
2. **Aromatic amino acid derivatives,** such as epinephrine, are water-soluble molecules derived from amino acids
3. **Peptides or Protein hormones:** These hormones are formed of:

   Large polypeptides: e.g. Insulin.

   Small polypeptides: e.g. ADH
4. **Fatty acid derivatives:** Prostaglandin

STEROIDS

Steroids comprise a group of cyclical organic compounds whose basis is a characteristic arrangement of seventeen carbon atoms in a four ring structure linked together from three 6-carbon rings followed by a 5-carbon ring and an eight-carbon side chain on carbon 17.



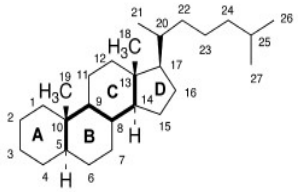
These drugs are used primarily in

1. Birth Control
2. Hormone-replacement Therapy HRT
3. Inflammatory Conditions
4. Cancer Treatment

STEROID NOMENCLATURE and BIOSYNTHESIS

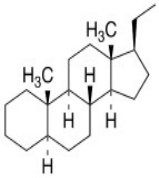
✓ Nearly all steroids are named as derivatives of:

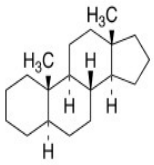
1. Cholestane
2. Pregnane
3. Androstane
4. Estrane

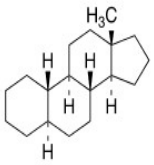


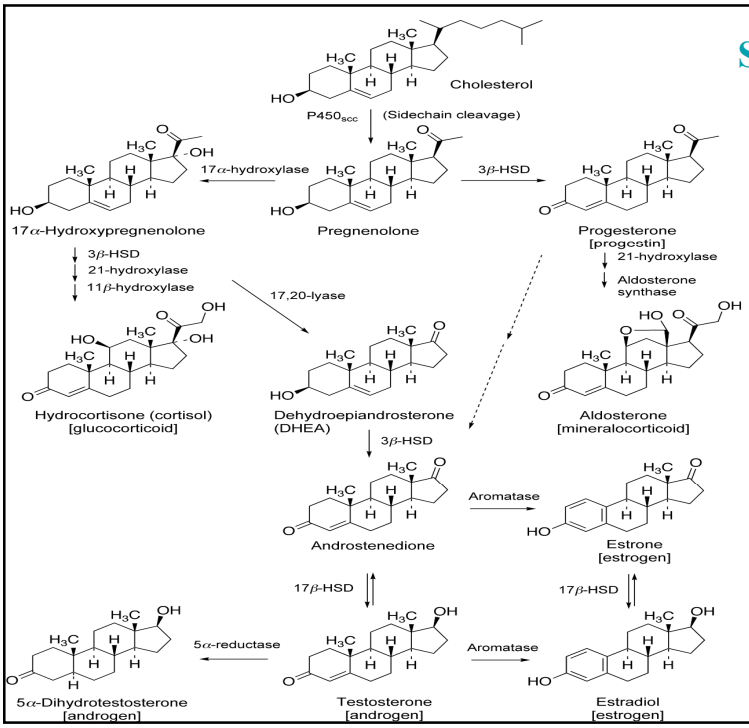
✓ There are Five general groups of Steroid Hormones :

1. Estrogens
2. Progestins
3. Androgens
4. Glucocorticoids GCs
5. Mineralocorticoids MCs









STEROID BIOSYNTHESIS

Steroid hormones in mammals are biosynthesized from cholesterol, which in turn is made in vivo from acetyl-coenzyme A (acetyl-CoA) via the **mevalonate pathway**.

Aldosterone and hydrocortisone are biosynthesized from pregnenolone through a series of steps involving hydroxylations at C11, C17, and C21 that convert pregnenolone to hydrocortisone.

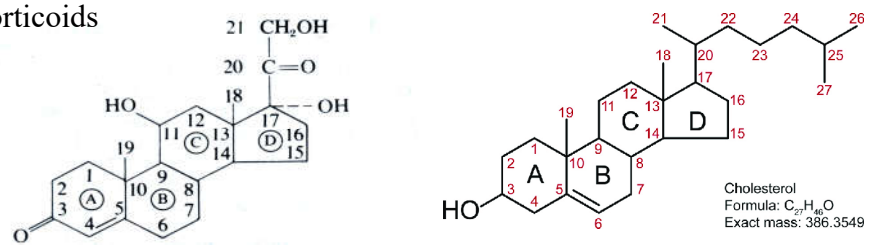
The 21-hydroxylase is important for the synthesis of both MCs and GCs.

Biosynthesis

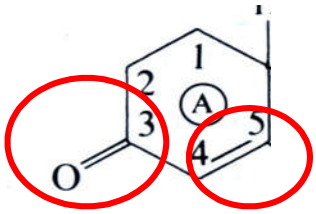
- Although humans do obtain approximately 300 mg of cholesterol per day in their diets, a greater amount (about 1 g) is biosynthesized per day.
- Although Steroid Hormones share a common structural foundation, the variations in the structures provide specificity for the unique molecular targets.
- Deficiencies in any of the enzymes cause congenital adrenal hyperplasia.

Steroids

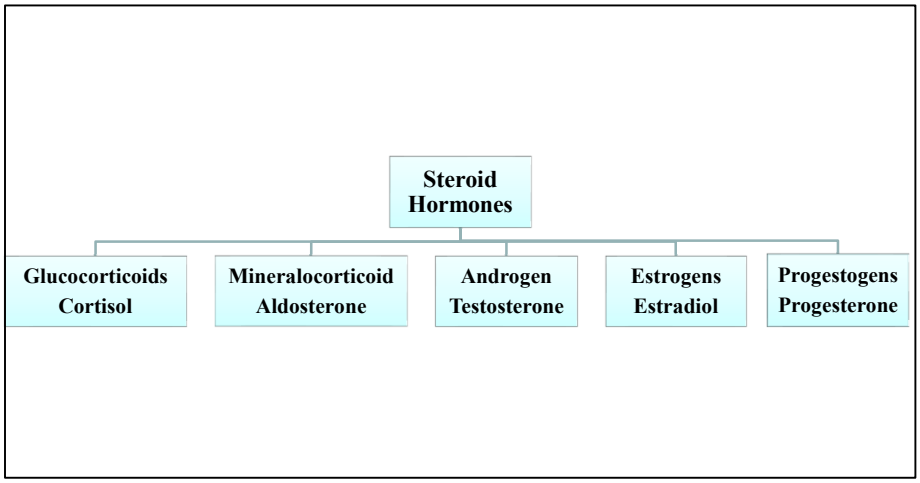
- Cholesterol have a 3-β-hydroxyl, and the branched 8-carbon side-chain at the 17- β position).
- However, there is a chemical nomenclature for each steroid that uniquely denotes the structure for that compound
- Steroid nucleus is the common structure; The keto group in C3, carbonyl group in C20, and the double bond between C4 & C5 are essential for both glucocorticoids & mineralocorticoids



All require 3 keto group and
4,5 unsaturation, **carbonyl group in C20**



Classes of Steroid Hormones



ADRENAL CORTEX HORMONES

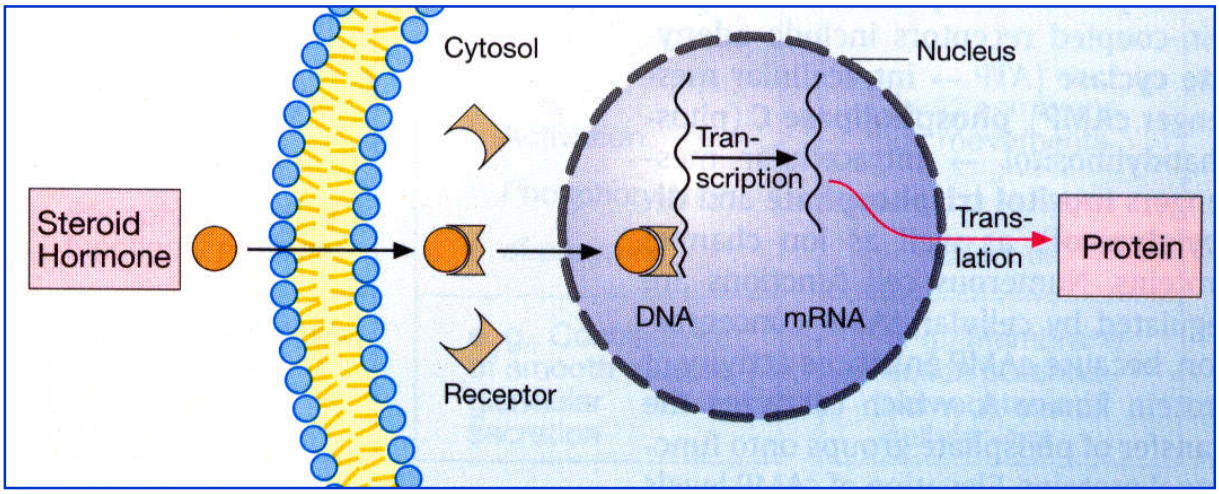
Endogenous Corticosteroids

- The adrenal glands (which lie just above the kidneys) secrete over 50 different steroids, including precursors for other steroid hormones.
- The most important hormonal steroids produced by the adrenal cortex, however, are aldosterone and hydrocortisone.
- Aldosterone is the primary Mineralocorticoid (MC) in humans (i.e., it causes significant salt retention).
- Hydrocortisone is the primary Glucocorticoid (GC) in humans (i.e., it has its primary effects on intermediary metabolism).

Biological Activities of Mineralocorticoids and Glucocorticoids

1. Aldosterone and, to a lesser extent, other MCs maintain a constant electrolyte balance and blood volume
2. GCs have key roles in controlling carbohydrate, protein, and lipid metabolism.
3. GCs have anti-inflammatory and immunosuppressive actions that arise through complex mechanisms.

Mechanism of Action of Steroid Receptors

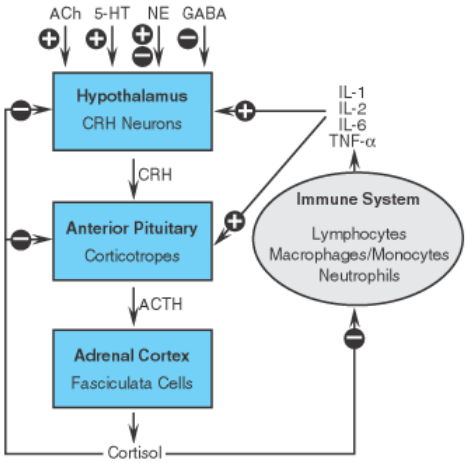


Glucocorticoids
Major Natural Glucocorticoids

- ✓ Glucocorticoids (GCs) are a class of corticosteroids, which in turn are a class of steroid hormones.
- ✓ Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor (GR).
- ✓ The name glucocorticoid (glucose + cortex + steroid) derives from its role in the regulation of the metabolism of glucose, its synthesis in the adrenal cortex.

Glucocorticoids
Major Natural Glucocorticoids

- ✓ The principal Glucocorticoids, Cortisol, is secreted by the adrenal cortex in response to internal or external stress
- ✓ Cortisol (or hydrocortisone) is the most important human glucocorticoid.
- ✓ It is essential for life, and it regulates or supports a variety of important cardiovascular, metabolic (carbohydrate& bone), immunologic (inflammatory responses) and homeostatic functions.

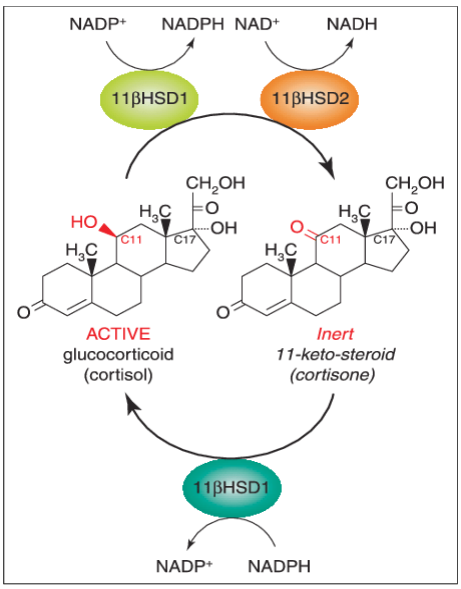


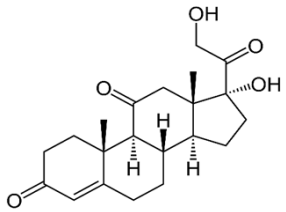
Natural Glucocorticoids

Interconversion of cortisol and cortisone by enzymatic oxidation or reduction at carbon position 11 (C11), catalyzed by the two cloned isoforms of 11-hydroxysteroid dehydrogenase (11HSD).

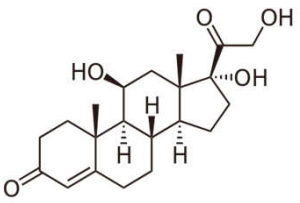
By convention, bonds below the plane of the molecule (bonds) are represented by dotted lines; bonds which have no definitive orientation are represented by solid lines; and bonds above the plane of the molecule (bonds) are represented by solid triangles.

Corticosterone and 11-dehydrocorticosterone have similar structures to cortisol and cortisone, respectively, but lack the -hydroxyl groups at position C17.





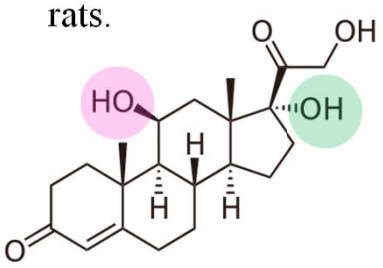
Cortisone



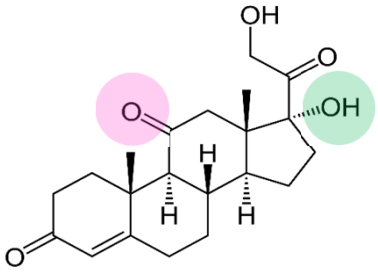
Cortisol (Hydrocortisone)

Cortisol is a 21-carbon steroid, a pregnane.

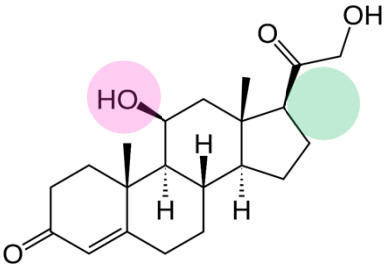
- Conversion of the 11β-hydroxyl to a ketone yields cortisone, an inactive metabolite of cortisol.
- The steroid that lacks the 17α- hydroxyl, corticosterone, has 70% lower glucocorticoid activity in humans, although it is the major glucocorticoid in rats.



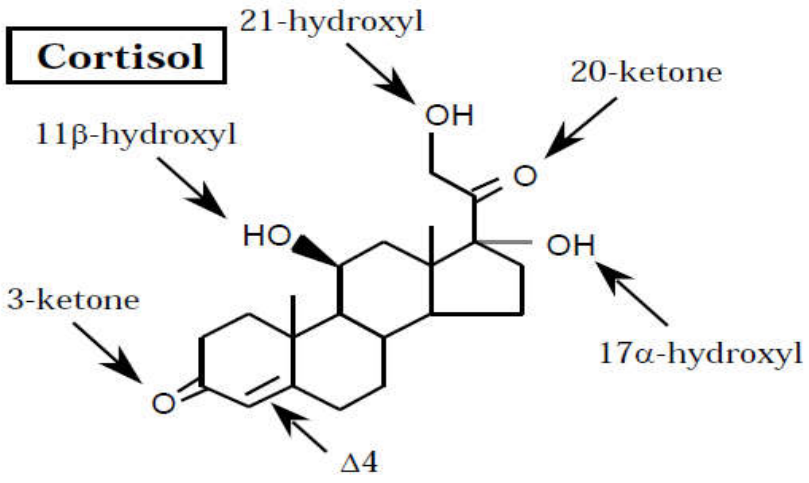
Cortisol (Hydrocortisone)



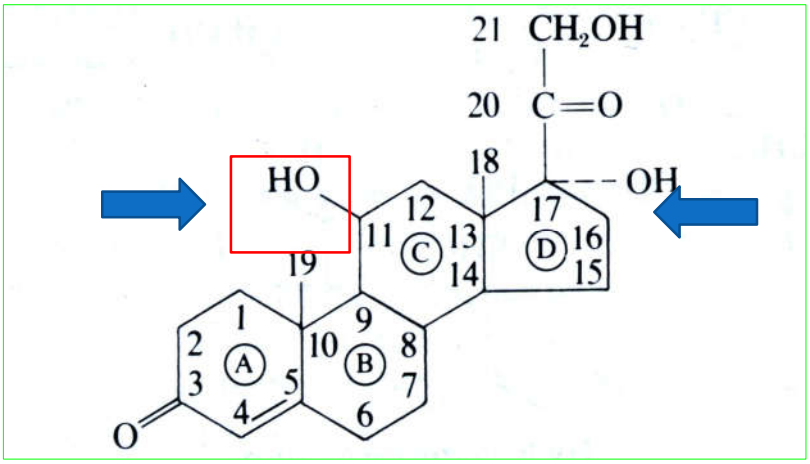
Cortisone



Corticosterone



Glucocorticoid activity requires 11 β hydroxyl (OH) group, an α-hydroxyl group linked to C17



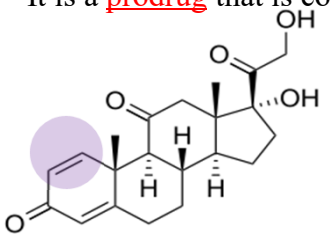
Synthetic Glucocorticoids

- ✓ They have the major function as Natural Glucocorticoids.
- ✓ These are used either as replacement therapy in glucocorticoid deficiency or to suppress the immune system and inflammation.
- ✓ They are usually more potent (5-100 times) & have less or no mineralocorticoids activity
- ✓ They are chemically more stable and administered as tablets, injections, creams & eye drops ….
- ✓ They are effective as an immuno-suppressant drug.

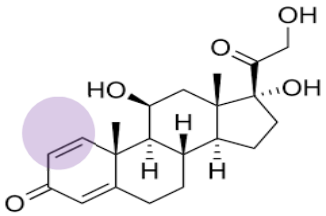
Synthetic Glucocorticoids

1. Prednisone:

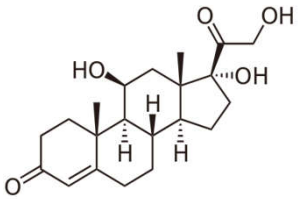
- Prednisone is a synthetic corticosteroid drug
- It is a prodrug that is converted in the liver to the active form, **Prednisolone**



Prednisone



Prednisolone



Cortisol

Prednisolone→ 6-methyl-prednisolone

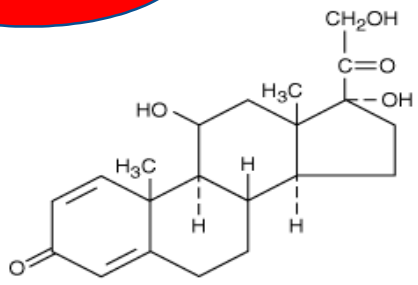
- 6-Methylcortisol has increased glucocorticoid and mineralocorticoid activity, whereas 6-methylprednisolone has somewhat greater glucocorticoid activity and somewhat less mineralocorticoid activity than prednisolone

Additional unsaturation of Ring A

Increase in GC activity

Slow metabolism

Glucocorticoid/ mineralocorticoid potency ratio

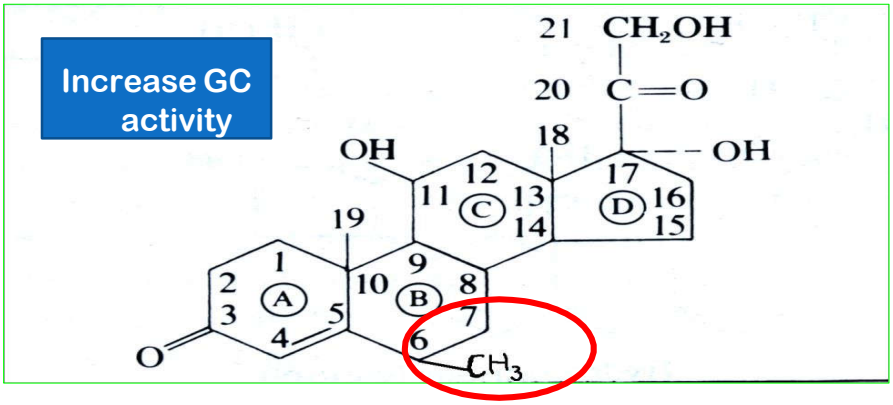


Prednisolone

Enhance Antiinflammatory effect

Salt retaining activity decreases

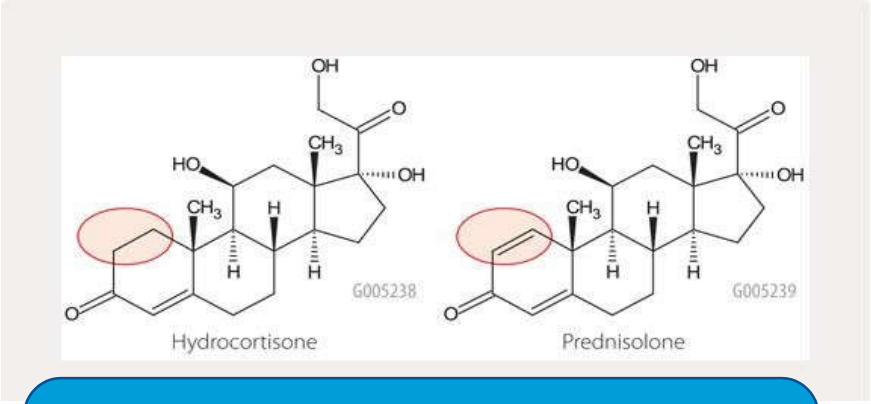
Increase GC activity



Unpredictable effects

6 α methyl cortisol - ↑GC & ↑MC activity

6 α methyl prednisolone - ↑GC & ↓ MC



- Increases glucocorticoid activity,
- Enhanced glucocorticoid/ mineralocorticoid potency ratio.
- Metabolized more slowly than hydrocortisone

Fluorinated Glucocorticoids

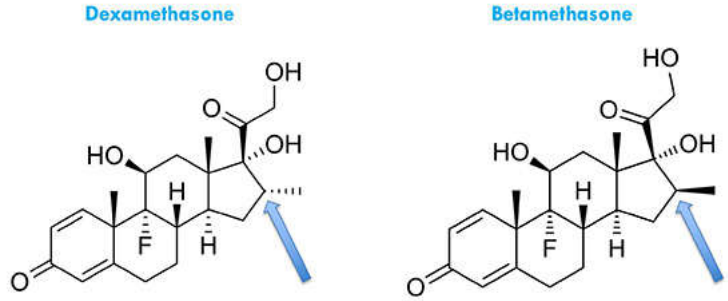
2. Betamethasone: *9 fluoro*

- Betamethasone doesn't cause water retention unlike other corticoids.
- It is used for rheumatoid arthritis, dermatitis, psoriasis, allergic conditions such as asthma and cancers such as leukemia.

3. Dexamethasone

✓It is the same as Betamethasone (16-beta to 16- alpha methyl modification)

✓It is more potent than natural corticosteroids (27 times) and prednisone (7 times).

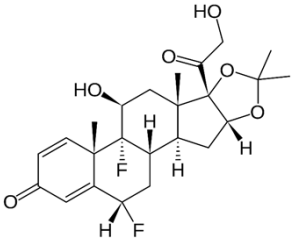


Betamethasone and dexamethasone have nearly the same molecular structure (differing by the chiral configuration of a single methyl group).

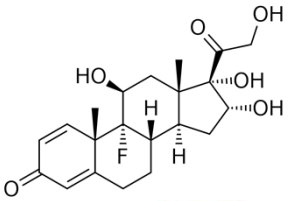
When combined with the 1-2 double bond in ring A plus other substitutions at C16 on ring D, the 9-fluoro derivatives formed (e.g., triamcinolone dexamethasone, and betamethasone) have marked glucocorticoid activity—the substitutions at C16 virtually eliminate mineralocorticoid activity

6α-fluoro has less salt retention properties than 9α- fluoro.

Fluocinolone

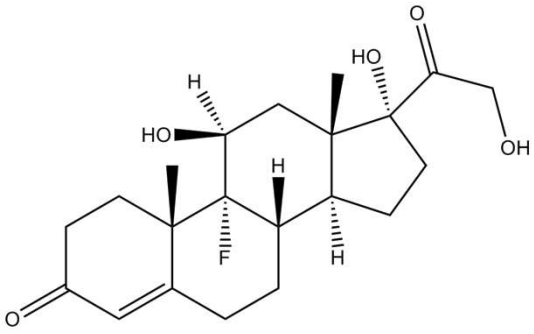


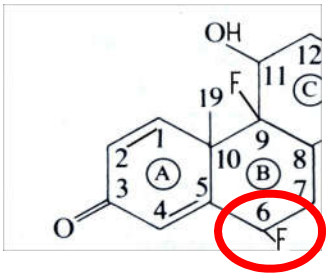
Triamcinolone



Fludrocortisone (9-fluorocortisol)

Enhanced activity at the GR (10 times relative to cortisol) greater activity at the MR (125 times relative to cortisol).

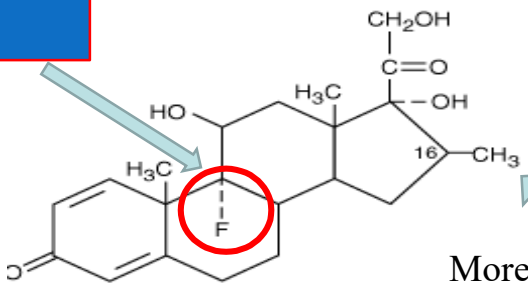




Fluorination at the 9 position on ring B enhances both glucocorticoid and mineralocorticoid activity, possibly related to an electron-withdrawing effect on the nearby 11-hydroxyl group. It is used in mineralocorticoid replacement therapy and has no appreciable glucocorticoid effect at usual daily doses of 0.05-0.2 mg.

9 α fluorination of RingB

Enhances GC & MC activity



Betamethasone

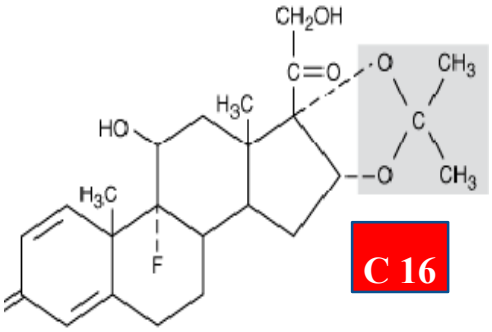
More GC activity & anti inflammatory activity
Eliminates MC activity

Hydrocortisone→fludrocortisone→dexamethasone & triamcinolone

1,2 double bond in ring A + other substitutions at C16 on ring D

the 9-fluoro derivatives

Anti-inflammatory effect enhances and salt- retaining effects weakens further.

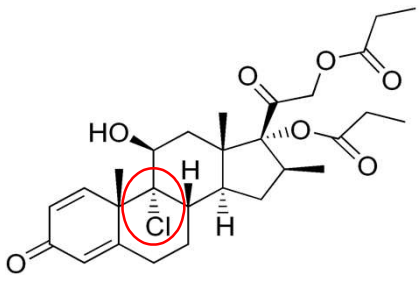


Triamcinolone (acetonide moiety shaded)

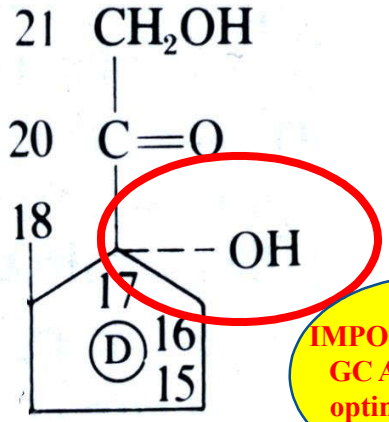
Acetonide b/w OH groups at C16 & C17

Chlorinated Glucocorticoids

- 9α-chloro derivative of betamethasone Beclomethasone dipropionate
- Increase stabilization
- Increase lipophilicity
- Increase bronchial tissue absorption
- Increase duration of action



17 α hydroxyl group on ring D- esterification of the hydroxyl group



IMPORTANT FOR GC ACTIVITY- optimal potency

- Acetonide b/w OH groups at C16 & C17
- Esterification of OH groups with Valerate at C17
- Esterification of OH groups with Propionate at C17 & C21
- Substitution of OH group at C21 with Chlorine

The steroids can be made more lipid soluble or more water soluble by making suitable ester derivatives of hydroxyl (OH) groups.

Derivatives with increased lipid solubility are often made to decrease the release rate of the drug from intramuscular (IM) injection sites (i.e., in depot preparations).

More lipid-soluble derivatives also have improved skin absorption properties and thus, are preferred for dermatological preparations.

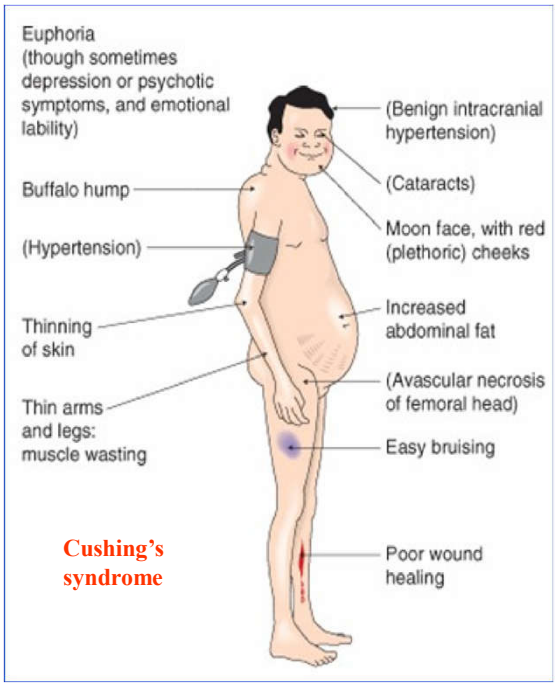
Derivatives with increased water solubility are needed for intravenous preparations

Contraindications

- Peptic ulcer
- Diabetes mellitus
- Hypertension
- Pregnancy (risk foetal defects)
- Psychosis
- Epilepsy
- Chronic heart failure
- Renal failure

Clinical uses:

- Allergic Rhinitis
- Rheumatoid Arthritis
- Asthma
- Multiple Sclerosis
- Carpal Tunnel Syndrome
- Gout
- Psoriasis
- Inflammatory Bowel Disease
- Sinusitis
- Lupus Erythematosus



Adverse effects of Glucocorticosteroids

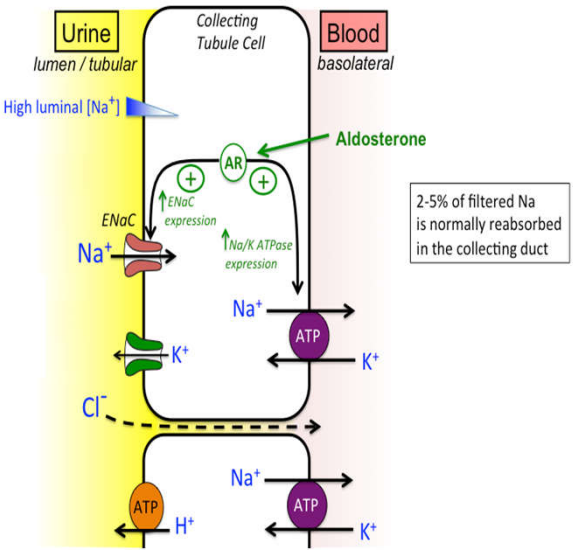
- **Cushing's syndrome**
- **Osteoporosis**
- **Tendency to hyperglycaemia**
- **Negative nitrogen balance**
- **Increased appetite**
- **Increased susceptibility to infections**
- **Obesity, etc.**

Mineralocorticoids

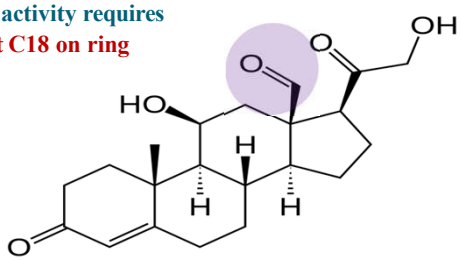
- ✓ Mineralo-Corticoids are a class of steroid hormones similar to aldosterone in their effects on salt & water balances.
- ✓ The name mineralocorticoids derives because these hormones are involved in the retention of sodium (Na), a mineral
- ✓ used mainly for treatment of **Addison disease**, or primary adrenal insufficiency.
- ✓ Aldosterone is primary endogenous mineralocorticoids
- ✓ Aldosterone is too expensive to produce commercially; therefore, other semisynthetic analogs have taken its place for treatment of Addison disease.
- ✓ Adding a 9-fluoro group to hydrocortisone greatly increases both salt retention and anti-inflammatory activity.

Mineralocorticoid (Aldosterone)
Detailed action mechanisms

- It acts on the mineralocorticoid receptors (MR) in the distal tubule & it upregulates and activates the Na+/K+ pumps, which reabsorbs three sodium ions into the blood and two potassium ions into the urine.
- This is in an increase of blood pressure & blood volume

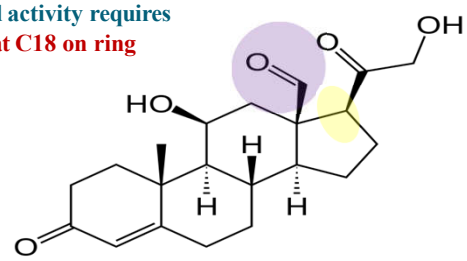


Mineralocorticoid activity requires
Aldehyde group at C18 on ring



Mineralocorticoid (Aldosterone)
Detailed action mechanisms

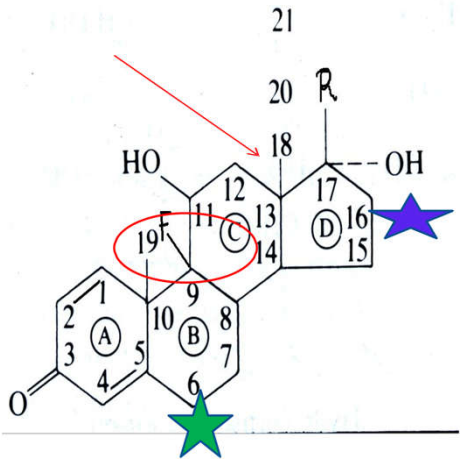
Mineralocorticoid activity requires
Aldehyde group at C18 on ring



- Aldosterone structurally very similar to cortisol, except that it lacks the 17a-hydroxyl group, and has an aldehyde at the 18-methyl.
- The 18-aldehyde is critical for mineralocorticoid activity; the sole difference between corticosterone and aldosterone is the 18-aldehyde, but aldosterone has 200 times higher mineralocorticoid activity than corticosterone.

Changes that alters mineralocorticoid activity

- Aldehyde group in the C18
- Fluorination at the 9α position on ring B
- 6α substitution on ring B
- Substitution at C16 on ring D



Changes that increase glucocorticoid activity

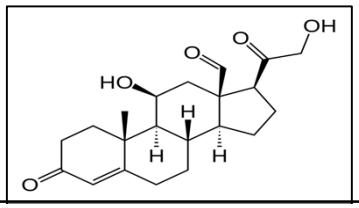
- Additional double bond b/w 1 & 2 carbon atoms
- Alpha methylation at 6th position
- Alpha fluorination at 9th position
- Substitution at 16th position

Structure activity relationships of mineralocorticoids

1. Highly active natural mineralocorticoids have no OH function in positions 17.

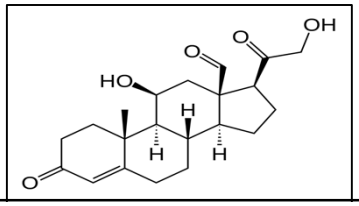
✓ In fact, OH groups in any position reduce the sodium-retaining activity of the adrenocorticoid.

2. 9α-F, 9α-Cl , and 9α-Br substitution causes increased retention of urinary sodium with an order of activity in which F > Cl > Br
3. Insertion of a 16α-OH group into the molecule affects the sodium retention activity so markedly that it not only negates the effect of the 9α-F atom but also causes sodium excretion



Structure activity relationships of mineralocorticoids

4. A double bond between positions 1 and 2 (C1-corticoids) also reduces the sodium retention activity of the parent drug. It contributes to the parent drug only approximately one-fifth the sodium-excreting activity of a 16α-OH group
5. A 17α-OH group reduces sodium retention as the unsaturation between positions 1 and 2.
6. Other substituents reported to inhibit sodium retention include 16α-CH3, 16β-CH3 and 16α-CH3O functions.

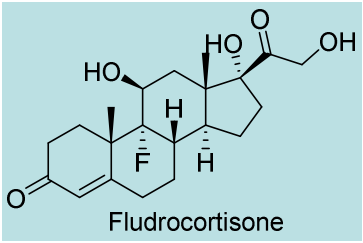


Mineralocorticoids related products

- ✓ There is no prescription products containing aldosterone as the active ingredient
- ✓ It is available mainly in analytical kits to estimate the levels of this hormone in patients
- ✓ The technique used is known as ELISA (enzyme linked immune sorbent assay) which is a wet lab type analytical biochemistry

Drugs used as mineralocorticoids
Fludrocortisone

- Fludrocortisone is used only for the treatment of Addison disease and for inhibition of endogenous adrenocortical secretions.
- It has up to about 800 times the MC activity of hydrocortisone and about 11 times the GC activity

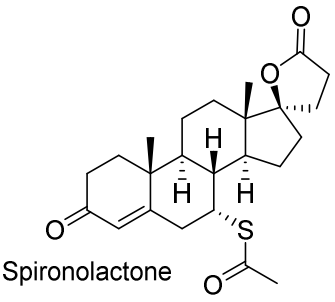


Fludrocortisone

Mineralocorticoids antagonists

Spironolactone

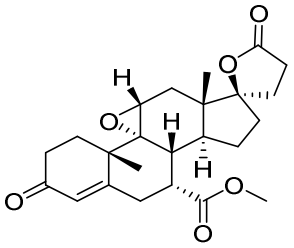
- It is a synthetic steroid that blocks mineralocorticoid receptors.
- It also blocks androgen, and blocks progesterone receptors.
- It belongs to a class of medications known as potassium-sparing diuretics.
- It is used as a diuretic and antihypertensive drug



Spironolactone

Eplerenone

It is similar to the diuretic spironolactone, though it is much more selective for the mineralocorticoid receptor in comparison (i.e., does not possess any antiandrogen, progestogen, glucocorticoid, or estrogenic effects)



Eplerenone