

Corticosteroids

§ You may have a fresh start any moment you choose, for this thing that we call failure is not the falling down, but the staying down §

The steroidal nature of adrenocortical hormones was established in 1937, when Reichstein synthesized desoxycorticosterone.

In humans, hydrocortisone (cortisol) is the main carbohydrate-regulating steroid, and aldosterone is the main electrolyte-regulating steroid

The mammalian adrenal cortex is divided into three concentric zones: the zona glomerulosa, zona fasciculata, and zona reticularis.

****A coronal section of the suprarenal gland****
Note how the adrenal cortex layers are arranged .
Most outer layer : zona glomerulosa
Intermediate: zona fasciculata
Most inner : zona reticularis

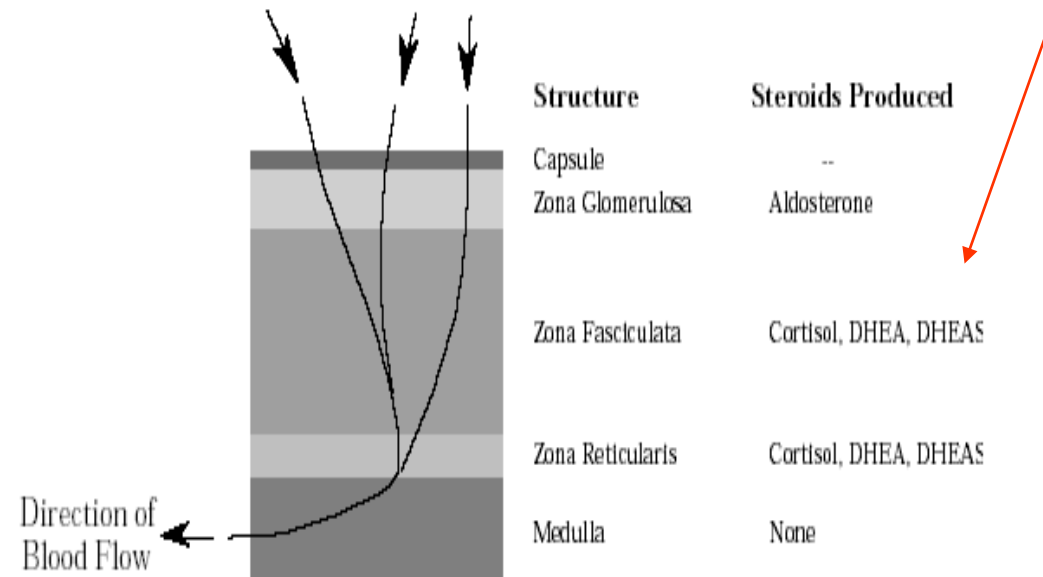
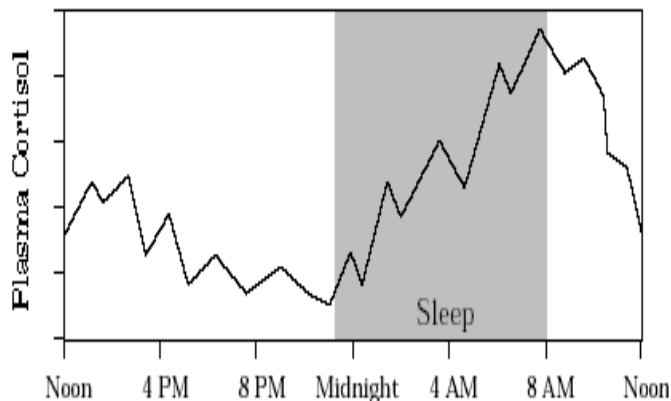
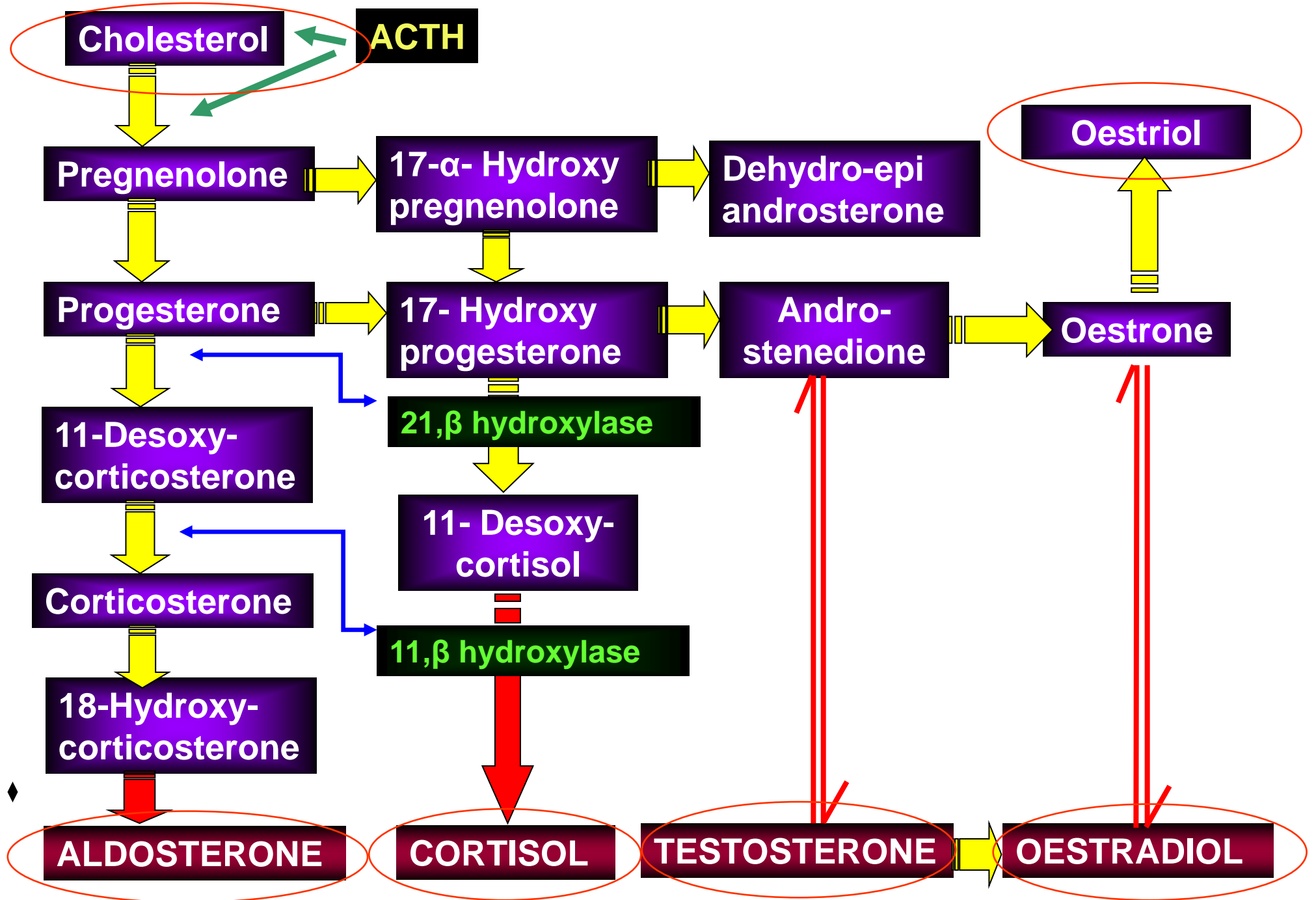


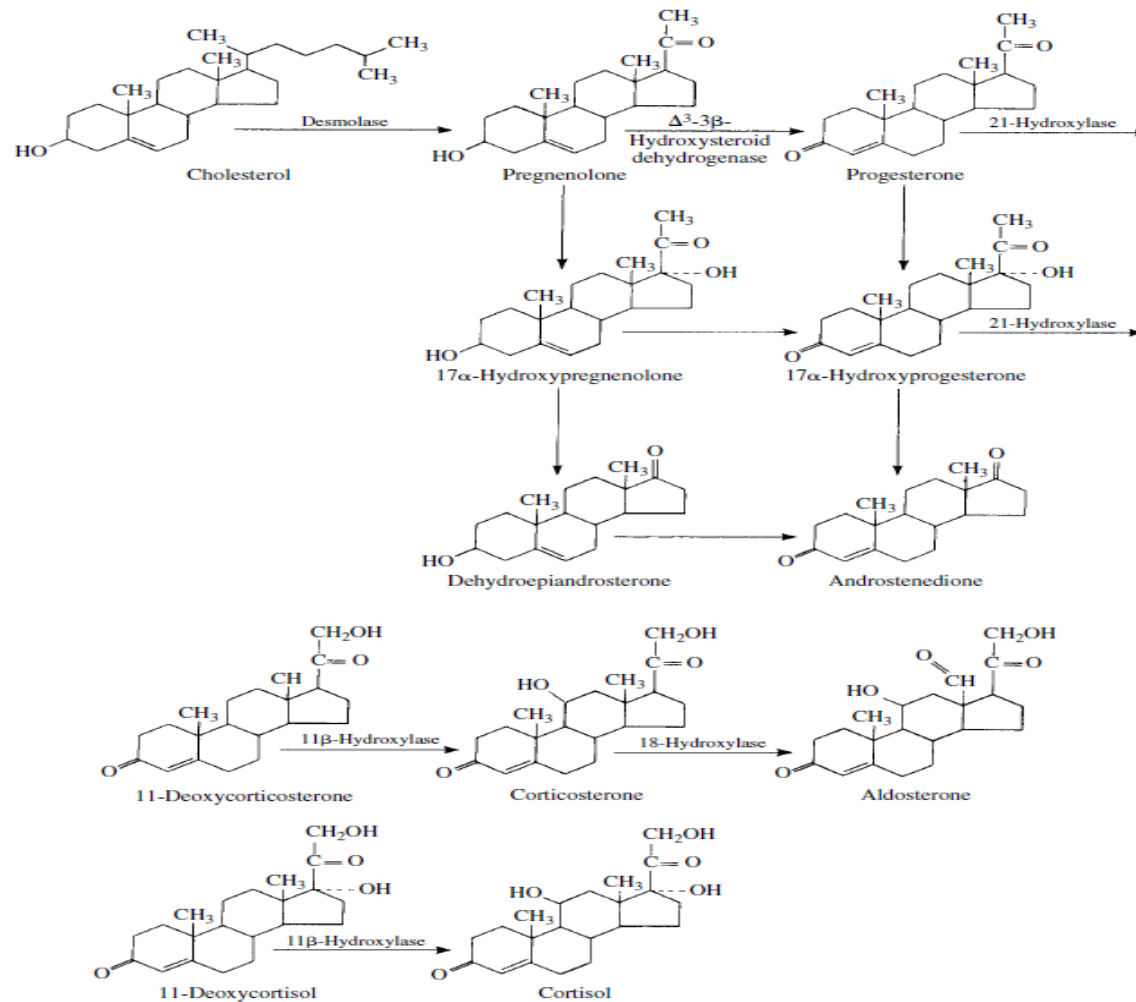
Figure 1. Cartoon of Adrenal Morphology.



It was mentioned in previous lectures that ACTH (tropic hormone produced in and released from the anterior pituitary) affects the adrenal gland and stimulates the conversion of cholesterol (the one and only precursor) into different steroidal hormones depending on the processing pathway it undergoes.

- The adrenal gland synthesizes steroids from cholesterol
- Cholesterol is transported into the mitochondria of steroidogenic tissue, where side chain cleavage is carried out

[**Important** : You are not supposed to know the detailed pathways by which cholesterol is converted into steroidal hormones in the adrenal gland .]



/*/ The processing of cholesterol mainly takes place in the mitochondria of the adrenocortical cells and after being cleaved and modified it gives off the steroidal hormones .

Synthetic Corticosteroids

The ultimate aim in altering the steroid molecule is to decrease sodium-retaining activity and to increase anti-inflammatory glucocorticoid activity

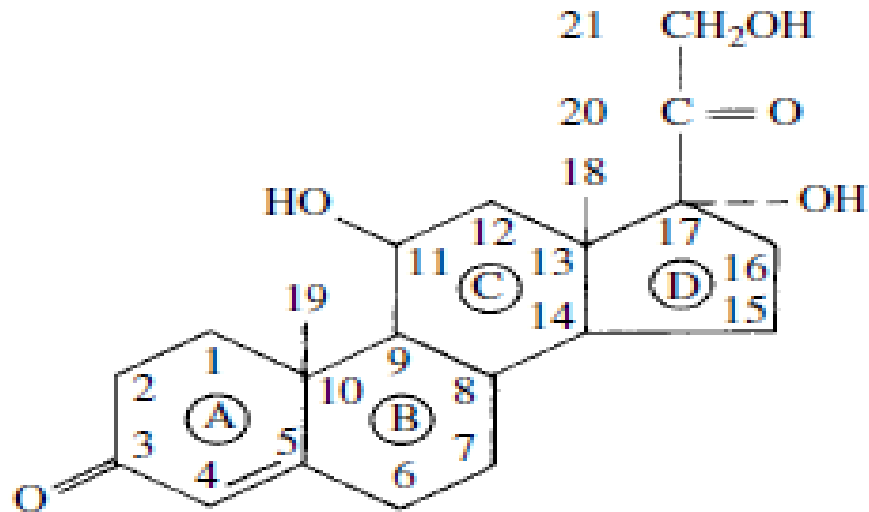


FIGURE 60.4
Basic corticosteroid nucleus.

/*/ Natural non - modified corticosteroids have their uses in the clinical field . Nevertheless , it was found that many aspects of the corticosteroids' activity can be enhanced and improved to avoid some undesired effects of which and promote certain desired ones . Starting from this point , scientists began modifying natural corticosteroids producing many synthetic corticosteroids that have less effect on sodium retention (decreased sodium retention > decreased water retention > less edema) and greater power as anti-inflammatory agents (increased anti-inflammatory activity)

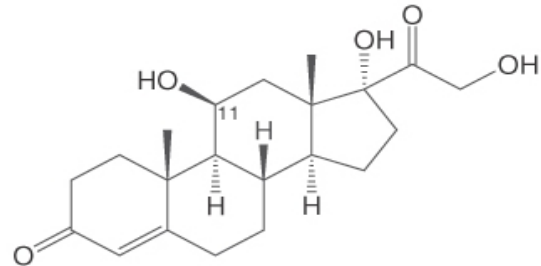
Glucocorticoid Analogues

**** Note :** You are not supposed to memorize the structure of these molecules **

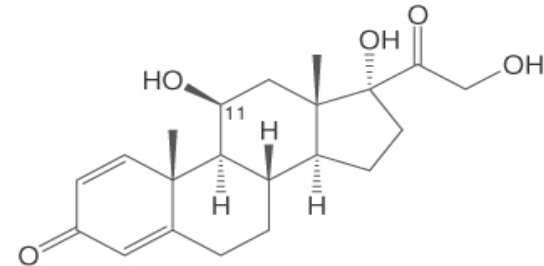
/* Have a quick look on these molecules .

/* Notice the modifications done on certain areas in the cortisol molecule to produce these different synthetic glucocorticoids analogs .

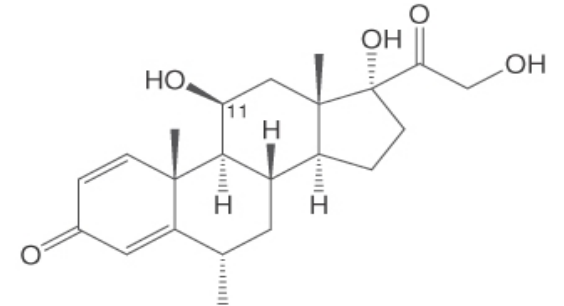
A



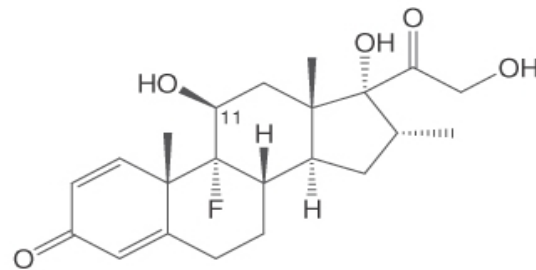
Cortisol



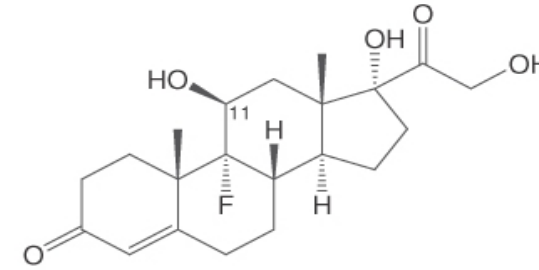
Prednisolone



Methylprednisolone

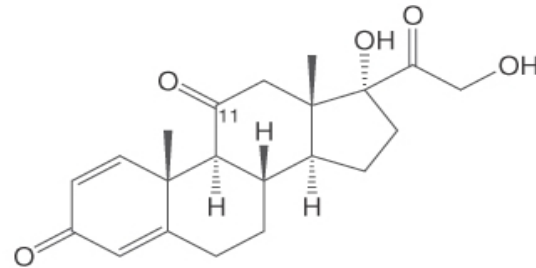


Dexamethasone

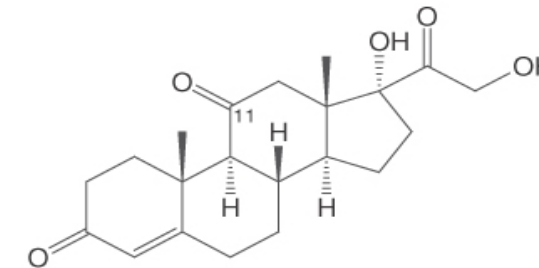


Fludrocortisone

B



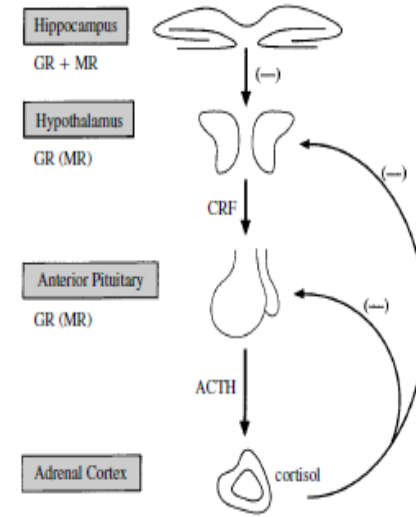
Prednisone



Cortisone

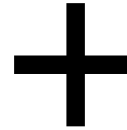
Negative feedback mechanism

- The role of the hypothalamic–pituitary axis in the regulation of adrenocortical hormone synthesis and release.
- The major physiological stimulus for the synthesis and release of glucocorticoids is corticotropin (ACTH) secreted from the anterior pituitary gland.



Glucocorticoids secretion:

- 1- Secretion of the releasing hormone from the hypothalamus (CRH)
 - 2- CRH exerts its effect on the anterior pituitary leading to the secretion of the stimulating hormone (ACTH)
 - 3- ACTH has an effect on all of the adrenal cortex layers but most prominently on the zona fasciculata (from which cortisol is secreted)
 - 4- ACTH stimulates the synthesis and secretion of the cortisol from zona fasciculata
 - 5- after cortisol finishes its job , no more cortisol secretion is needed , accordingly cortisol negatively feedbacks it's own secretion by inhibiting either hypothalamus or anterior pituitary (long loop negative feedback)
- Note : the doctor referred to the inhibition of the anterior pituitary by cortisol as short loop negative feedback :')



What's the role of the hippocampus in this whole thing ? (additional)

As you see the hippocampus plays an inhibitory role .

The hippocampus is strongly involved in the regulation of the stress response (I.e : it has many stress hormones sensitive receptors) by exerting negative feedback on the hypothalamic-pituitary-adrenal axis .

Note : the doctor said that the hypothalamus is stimulated by signals from the hippocampus and this is incorrect scientifically

Pharmacological Actions

- The pharmacological actions of steroids are generally an extension of their physiological effects
- Glucocorticoids (e.g., prednisolone) used to suppress inflammation, allergy and immune responses.
- Anti-inflammatory therapy is used in many illnesses (e.g., RA, UC, BA, eye and skin inflammations).
- tissue transplantation and lymphopoiesis (leukemias and lymphomas).
- Striking improvements can be obtained, but **severe adverse effects** are ensue.

/1/ The most important use of the synthetic glucocorticoids is as anti-inflammatory agents (immune suppressors)

/2/ Glucocorticoids are also used after organ transplantation to prevent organ rejection by the immune system .

/3/ However, and despite the satisfactory actions of glucocorticoids analogs in the cases of exaggerated immune responses , allergy , and inflammation , they have serious adverse effects .

Pharmacological Actions

Again , remember that the synthetic glucocorticoids analogs are preferred over natural glucocorticoids because they :

- 1- decrease sodium and water retention (decrease steroids - induced edema)
- 2- have better anti- inflammatory activity
- 3- have higher affinity to glucocorticoids receptors and are more specific and better directed towards their jobs within the body .

- For most clinical purposes, synthetic glucocorticoids are used because they have a higher affinity for the receptor, are less activated and have little or no salt-retaining properties.
- **Hydrocortisone** used for: orally for replacement therapy, i.v. for shock (**allergic shock**) and asthma, topically for eczema (ointment) and enemas (ulcerative colitis).
- **Prednisolone** the most widely used drug given orally in inflammation and allergic diseases.

Pharmacological Actions

- **Betamethasone** and **dexamethasone**: very potent, w/o salt-retaining properties; thus, very useful for high-dose therapies (*e.g.*, cerebral edemas).

No salt retaining properties which allows their use in high concentrations

- **Beclometasone**, **dipropionate**, **budesonide**: pass membranes poorly; more active when applied topically (severe eczema for local anti-inflammatory effects)

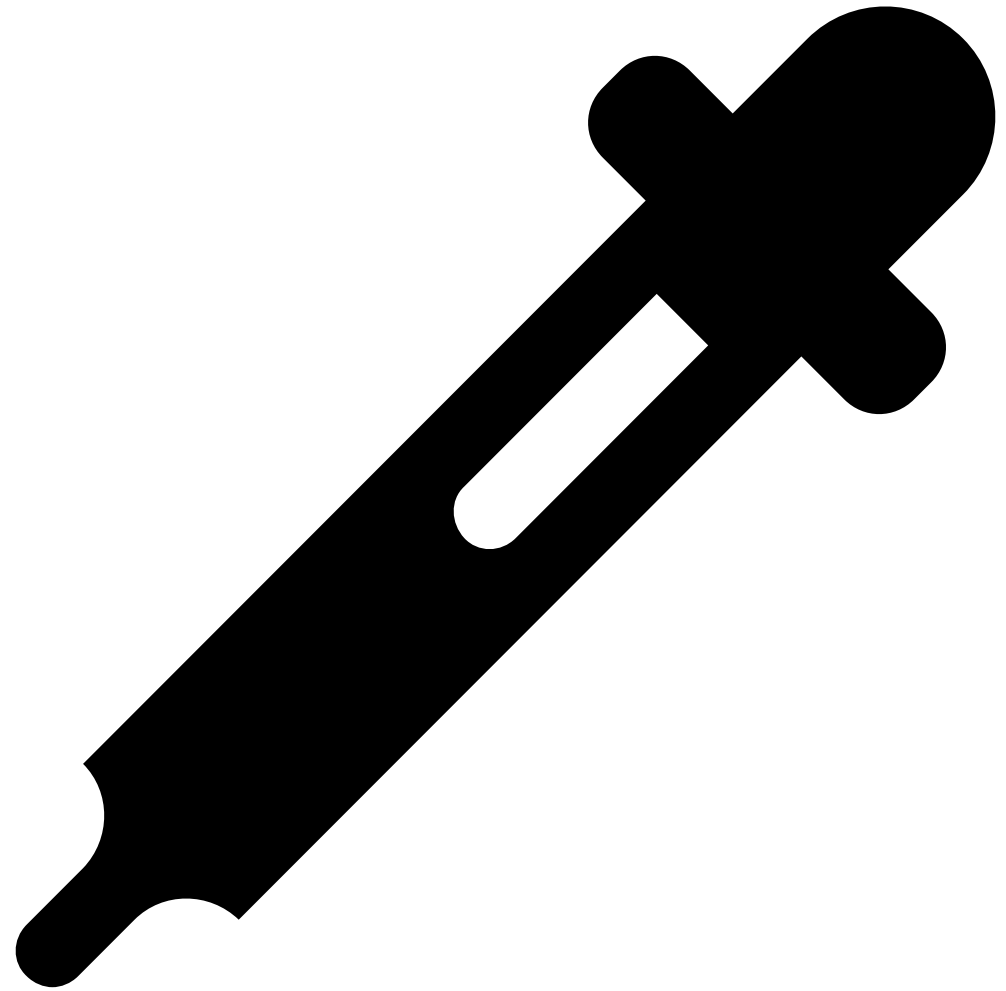
Why ? Because topical agents aren't made for the sake of membranes crossing ; they have localized limited effects

than orally; used in asthma, (aerosol).

Why aerosol ? Again because it has low permeability potential and low membrane crossing ability so when used this way there will be no need for penetration or any of the aforementioned crossing requirements


- **Triamcinolone**: used for severe asthma and for local joint inflammation (intra-articular inj.).

ACTIONS OF THE
CORTICOSTEROIDS



Carbohydrate, Protein, and Fat Metabolism

- The glucocorticoids increase blood glucose and liver glycogen levels by stimulating gluconeogenesis.
- The source of this augmented carbohydrate production is protein
- the protein catabolic actions of the glucocorticoids result in a negative nitrogen balance.
- The inhibition of protein synthesis by glucocorticoids brings about a transfer of amino acids from muscle and bone to liver, where amino acids are converted to glucose.



Inhibit proteins synthesis and activate proteins breakdown resulting in increased amino acids mobilization from muscles and bones to the liver .

Collectively : increased serum glucose & free amino acids (proteins breakdown) levels

Electrolyte and Water Metabolism

- Another major function of the adrenal cortex is the regulation
- of water and electrolyte metabolism.

- The steroid-binding specificity of mineralocorticoid and glucocorticoid receptors overlaps in the distal cortical cells and collecting tubules, so that glucocorticoids may mediate mineralocorticoid-like effects

Mineralocorticoid can increase the rate of sodium reabsorption and potassium excretion severalfold. This will occur physiologically in response to sodium or volume depletion or both. The primary site of this effect is the distal tubule

We already know from this system's physiology course that :

§ Glucocorticoids (major : cortisol) are mainly used in metabolism

§ Mineralocorticoids (major : aldosterone) are mainly used in achieving electrolytes balance (sodium retention / potassium excretion / water retention) .

However , this doesn't hide the fact that both cortisol and aldosterone have contributions in achieving electrolytes balance and regulating metabolism respectively.

How ?

Generally each of these two hormones has its own well defined specificity towards certain receptors , but and impressively these two hormones steroid - binding specificity overlaps in the distal cortical cells and collecting ducts of the kidney . As a result for this overlap , glucocorticoids (cortisol) acquire the ability of binding to mineralocorticoids' receptors having by this an effect on sodium and water retention .

Cardiovascular Function

- Glucocorticoids directly stimulate cardiac output and potentiate the responses of vascular smooth muscle to the pressor effects of catecholamines and other vasoconstrictor agents.
- The presence of steroid receptors on vascular smooth muscle suggests a direct effect on vasomotor activity.
- *Thus, corticosteroids appear to play an important role in the regulation of blood pressure by modulating vascular smooth muscle tone*

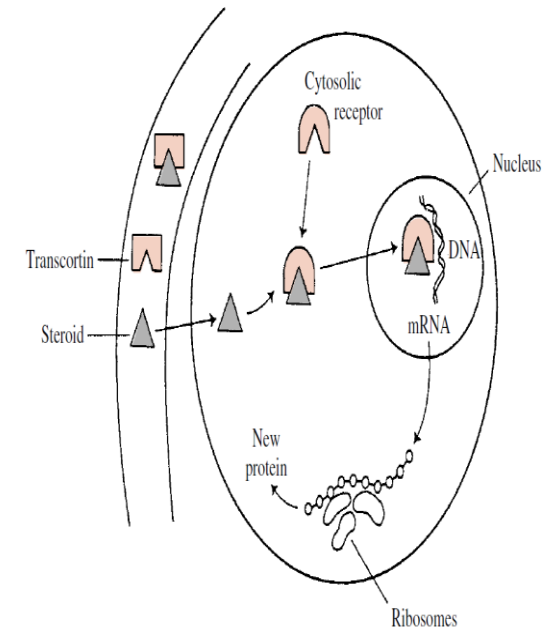
Collectively: Glucocorticoids increase blood pressure by increasing cardiac output and inducing vasoconstriction.

- Steroids transported by transcortin enter the target cell by diffusion and then form a complex with its cytosolic receptor protein.

- Glucocorticoids bind to cytoplasmic glucocorticoid receptors containing two subunits of the heat shock protein that belong to the 90-kDa family.

- The heat shock protein dissociates, allowing rapid nuclear translocation of the receptor–steroid complex.

- Within the nucleus, the glucocorticoid receptor induces gene transcription by binding to specific sequences on DNA called glucocorticoid response elements in the promoter– enhancer regions of responsive genes



/*/ Glucocorticoids are steroid hormones so obviously they have their receptors inside cells .

/*/ When a glucocorticoid enters the cell it binds to its receptor in the cytoplasm, then the receptor - substrate complex enters the nucleus where it binds to a certain consequence on the DNA molecule called “ glucocorticoid responsive element “ .

This binding induces transcription of particular genes so that the resulting mRNAs are then translated to different proteins that induce changes within the cell and lead to further production of regulatory proteins .

- Metabolites of arachidonic acid, including prostaglandins (PG), thromboxanes, and leukotrienes, are considered strong candidates as mediators of the inflammatory process.

- Steroids may exert a primary effect at the inflammatory site by inducing the synthesis of a group of proteins called lipocortins. These proteins suppress the activation of phospholipase A2, thereby decreasing the release of arachidonic acid and the production of proinflammatory effect

- Another possible glucocorticoid-sensitive step is the PG endoperoxide H synthase (or cyclooxygenase) (COX) mediated conversion of arachidonate to PG endoperoxides

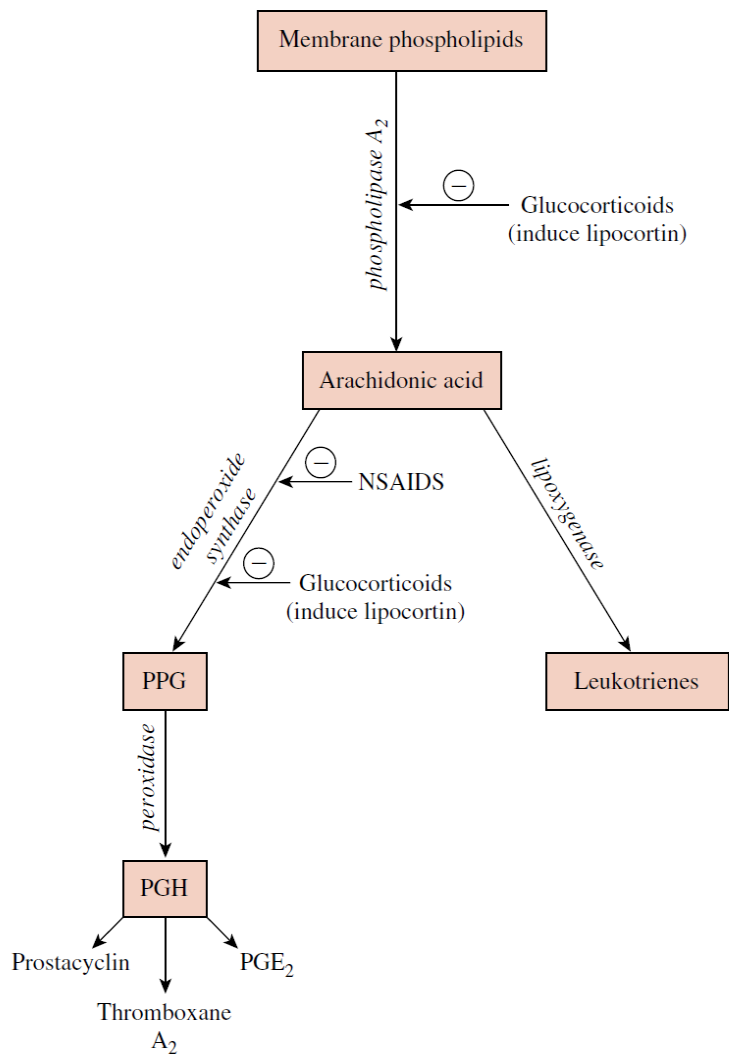


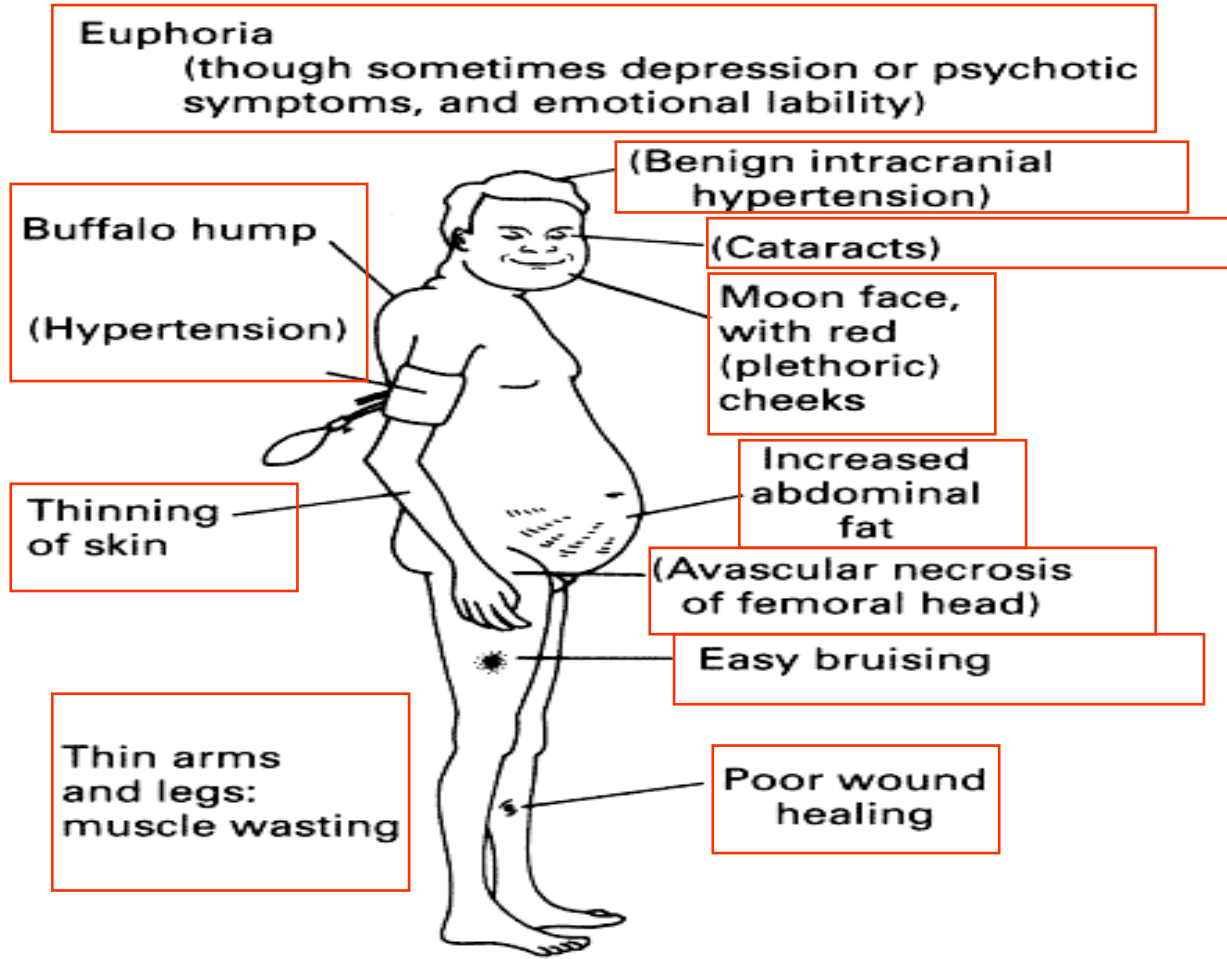
FIGURE 60.6 Possible site or sites of action of glucocorticoids on prostanoid production.

**** Immunosuppressive effect of the glucocorticoids:
Membrane phospholipids > (Phospholipase A₂) > Arachidonic acid**

**Arachidonic acid > (cyclooxygenases) > Prostaglandins
OR
Arachidonic acid > (lipoxygenase) > leukotrienes**

**** Glucocorticoids can inhibit both phospholipase A₂ (inhibiting both prostaglandins and leukotrienes synthesis) and cyclooxygenases (inhibiting only prostaglandins synthesis)**

Steroids adverse effects



Also:

Osteoporosis
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
Increased susceptibility to infection
Obesity

IMPORTANT

Those undesirable adverse effects are more associated with oral & IV administration of glucocorticoids rather than topical and aerosol administration.

THERAPEUTIC
USES OF
STEROID
HORMONES



Replacement Therapy

- Adrenal insufficiency may result from hypofunction of the adrenal cortex (primary adrenal insufficiency, Addison's disease) or from a malfunctioning of the hypothalamic–pituitary system (secondary adrenal insufficiency).
- In treating primary adrenal insufficiency, one should administer sufficient cortisol to diminish hyperpigmentation and abolish postural hypotension; which are the cardinal signs of Addison's disease.

Addison's disease : insufficient concentrations of steroidal hormones

***** There is no sufficient amounts of glucocorticoids and this explains the need for the exogenous administration of glucocorticoids. (the drug of choice for replacement therapy)**

Inflammatory States

- glucocorticoids possess a wide range of effects on virtually every phase and component of the inflammatory and immune responses,
 - they have assumed a major role in the treatment of a wide spectrum of diseases with an inflammatory or immune-mediated component.

 - Rheumatoid arthritis is the original condition for which antiinflammatory steroids were used,
 - Intraarticular glucocorticoid injections have proven to be efficacious, particularly in children.
- However,*
- the detrimental effects of glucocorticoids on growth are significant for children with active arthritis.
 - steroids offer symptomatic relief from this disorder by abolishing the swelling, redness, pain, and effusions,
they do not cure
 - Progressive deterioration of joint structures and the disease process may be exacerbated after steroid therapy is terminated

IMPORTANT

Glucocorticoids intake must be carefully dosed for patients especially children to avoid as much as possible of their serious adverse effects (one of the most important adverse effects : inhibition of growth in children)



It is good to have an end to
journey towards; but it is the
journey that matters, in the end