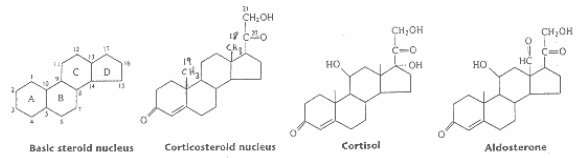
Glucocorticosteroids



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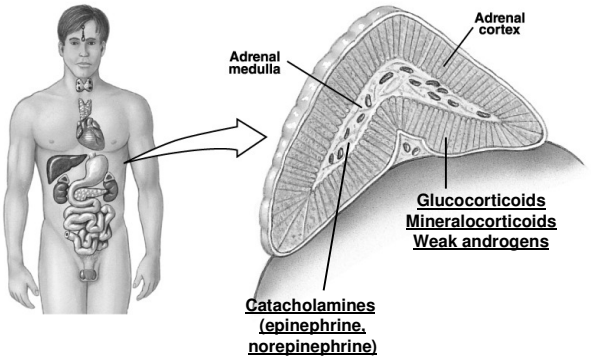
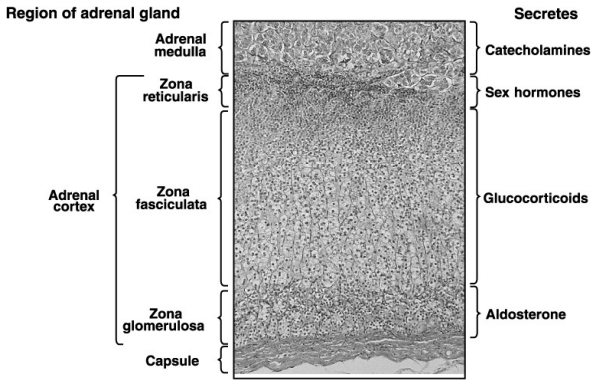
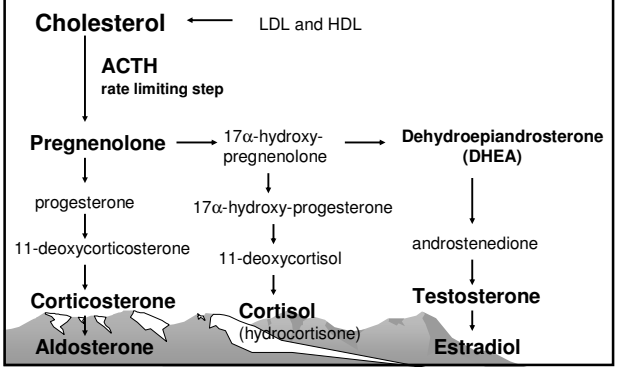
Adrenal Gland





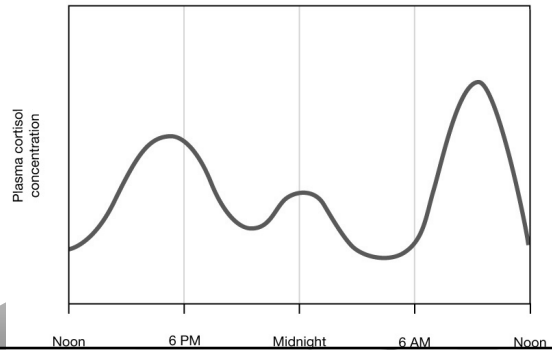
Corticosteroid and Sex Hormone Biosynthesis



Glucocorticoids

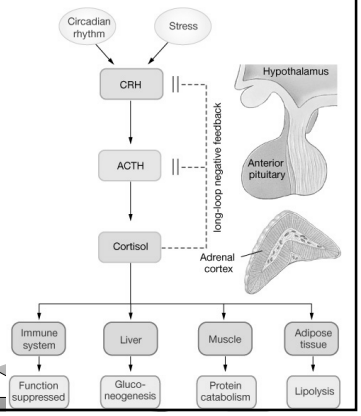
- Not stored
  Rate synthesis = rate release.
- Synthesized rhythmically
  - Controlled by irregular pulses of ACTH
  - Influenced by light
  - Major pulses early in morning and after meals.

Circadian rhythm of cortisol secretion



Control of Cortisol Secretion: Feedback Loops

- External stimuli
- Hypothalamic
- Anterior Pituitary
- Adrenal cortex
- Tissues

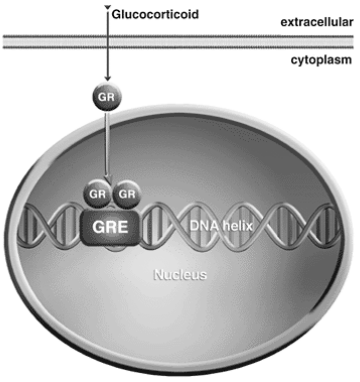


Glucocorticosteroids
Mechanism of action:

- All steroids stimulate the **transcription** of selected genes.
- These genes then mediate the synthesis of particular **proteins**, which again bring about **cellular** effects.
- At steroid-sensitive tissue there is a specific corticosteroid-binding protein receptor in the cytoplasm. The receptor is then activated by the steroid.

Glucocorticosteroids
Mechanism of action:

- A DNA-binding domain will then be exposed. The steroid-receptor-complex then binds with the DNA.
- An increase in RNA-polymerase activity then follows and specific messenger-RNA is formed.
- The synthesis of polypeptides follows.
- In the case of the glucocorticosteroids it is **lipocortin**.



Glucocorticosteroids

The effects of glucocorticosteroids:

A. Effect on fluid balance, electrolyte balance, glucose and protein metabolism.

B. Anti-inflammatory and immune-suppressive.

C. Negative feedback on anterior hypophysis and thalamus.

Glucocorticosteroids

A. <u>Effects on fluid balance & electrolytes:</u>

- It causes **sodium retention** and **potassium loss** with the resultant effect on fluid balance.
- It **decreases absorption** of **calcium** from the **GI** tract and an **increased** excretion through the kidneys.
  - The effect of this is a higher incidence of **osteoporosis**.

Glucocorticosteroids

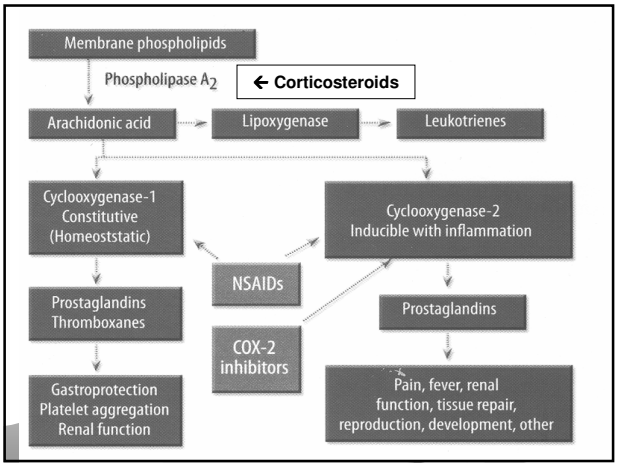
Effects glucose and protein metabolism:

- **Decreased uptake and utilisation** of glucose through cells.
- **Increased** gluconeogenesis → **hyperglycaemia**.
- An **increase in glycogen storing** probably due to an **increase in insulin secretion** in response to hyperglycaemia.
- **A decrease in protein synthesis** and an increase in the breakdown of protein, especially muscles.

Glucocorticosteroids

B. <u>Suppresses all types of inflammotary responses</u>:

- **COX-2 expression** is suppressed with a decrease in prostaglandins.
- A decrease in **platelet activating f**actor, which is important in allergic and inflammatory responses.
- A decrease in the formation of a few **leukotrines** and **tumour necrosis factor α.**
- It decreases the **proliferation of T-cells** and the migration of inflammatory cells → an impaired cell-mediated immunity. **Large** doses suppress **antibody production.**



Glucocorticosteroids

Uses:

- Replacement therapy in **adrenal insufficiency**.
- Daily oral dose varies between 20 and 40mg daily, but should really be calculated to correlate with body surface => 50mg for a large man. In primary adrenal failure mineralocorticosteroids must be added.
- Respiratory diseases:
  - **Asthma**
  - Allergic **rhinitis**
  - **Sarcoidosis** in severe disease
  - **Tuberculosis** to control the inflammatory response.

Glucocorticosteroids

Uses:

- Rheumatoid and collagen diseases **like SLE, rheumatoid arthritis**, etc.
- Inflammatory skin diseases. Eczematous **dermatitis** is effectively treated with the stronger halogenated corticosteroids, but **methylprednisolone aceponate** is as effective without the possibility of systemic absorption, due to its pharmacokinetics.
- As part of **oncotherapy** and organ **transplantation.**

Glucocorticosteroids

Uses:

- **Liver** diseases like chronic active hepatitis, fulminating hepatitis and subacute hepatic necrosis to improve survival.
- Diseases of the **GIT**, like Crohn'disease and ulcerative colitis.
- **Nephrotic** syndrome.

Glucocorticosteroids
Uses:

- **Brain oedema due to inflammatory** processes, but not when it is due to cell damage secondary to cardiogenic or thrombo-embolic incidences.
- **Hypercalcaemia** in **sarcoidosis**(inhibit calcium absorption) and **myelomatosis**(increase calcium excretion).

Glucocorticosteroids
Side-effects:

- **CNS:**
  - Depression, anxiety, euphoria, schizophrenia. Psychological abnormalities ranging from mania to depression.
- Glaucoma.
- **Skin:**
  - Thin skin, bruising easily. Hirsutism, acne, because of increase in androgen metabolism. Striae.
- **Atrophy:** Muscles, bone and lymph glands.

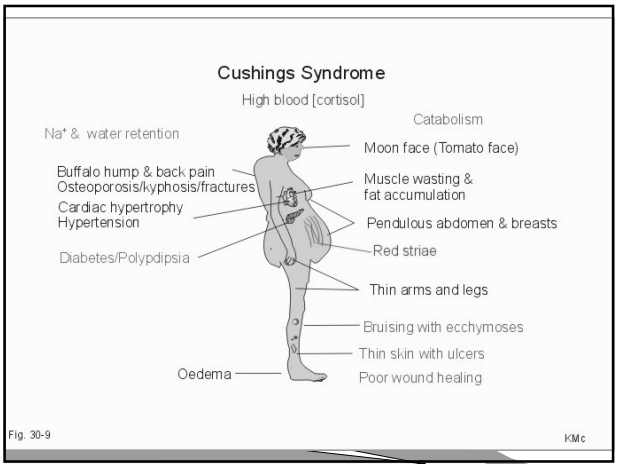
Glucocorticosteroids
Side-effects:

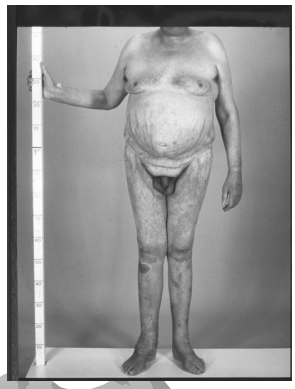
- Hyperglycaemia and an increase in glycogen with the development of **diabetes mellitus.**
- **Sodium and fluid retention:**
  - Hypertension
  - Oedema
  - Congestive heart failure.
- **Bleeding stomach ulcers.**
- **Potassium loss:** → Muscle weakness and hypokalaemic alkalosis.

Glucocorticosteroids

Side-effects:

- Release of antigrowth hormone to inhibit growth.
- Redistribution of fat.
- Adrenal insufficiency after prolonged use:
  - Therapy should slowly be withdrawn after a period of prolonged use over at least a month.





Compound	Potency	Equivalent in mg	Na retention	Comment and usage
Cortisol	1	20mg	2+	Use in emergency and replacement.
Cortisone	0,8	25mg	2+	Cheap. Converted to hydrocortisone before effect takes place. Serious mineralocorticoid effects. Seldom used.
Corticosterone	O,3		15+	Not used.
Prednisolone	4	5mg	1+	Drug of choice for systemic anti-infl and immune suppression.
Prednisone	3,5	5mg	1+	Inactive. Must be converted to Prednisolone to become active. Anti-inflammatory and immune suppressive.
Methylprednisolone	5	4	0	Anti-inflammatory and immune suppressive.
Triamcinolone	5		0	More toxic. Anti-inflammatory and immune-suppressive.
Dexamethasone	30	0,75	0	Anti-inflammatory and immune-suppressive. Used for cerebral oedema and ACTH suppression.
Betamethasone	26	0,6	0	Same as above.
Beclomethasone	+			Topical and inhalation.
Budesonide	+			As above.