Al-Mustaqbal University College

Pharmacy Department / Second Stage

PHYSIOLOGY II

ENDOCRINE, L3

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Adrenal glands

The two adrenal glands, each of which weighs about 4 grams, lie at the superior poles of the two kidneys. Each is composed of two distinct functional regions:

Adrenal medulla **Adrenal cortex**

The adrenal medulla

is the central part of the adrenal gland, surrounded by the cortex. The medulla plays a very important role in homeostasis: it serves to secrete **epinephrine (adrenaline**) and **norepinephrine (noradrenaline)**. The main secreting cells of the adrenal medulla are called **chromaffin** cells, which are neuroendocrine cells that are modified sympathetic ganglia. The chromaffin cells are **neural crest cell** derivatives. **Adrenaline** is released in response to activation of the **sympathetic nervous system**, fibres of which are carried to the adrenal medulla by the thoracic splanchnic nerves. Both adrenaline and noradrenaline are produced from the amino acid **tyrosine,** through multiple reactions.

It also has other secretory functions such as the production of **dopamine**.

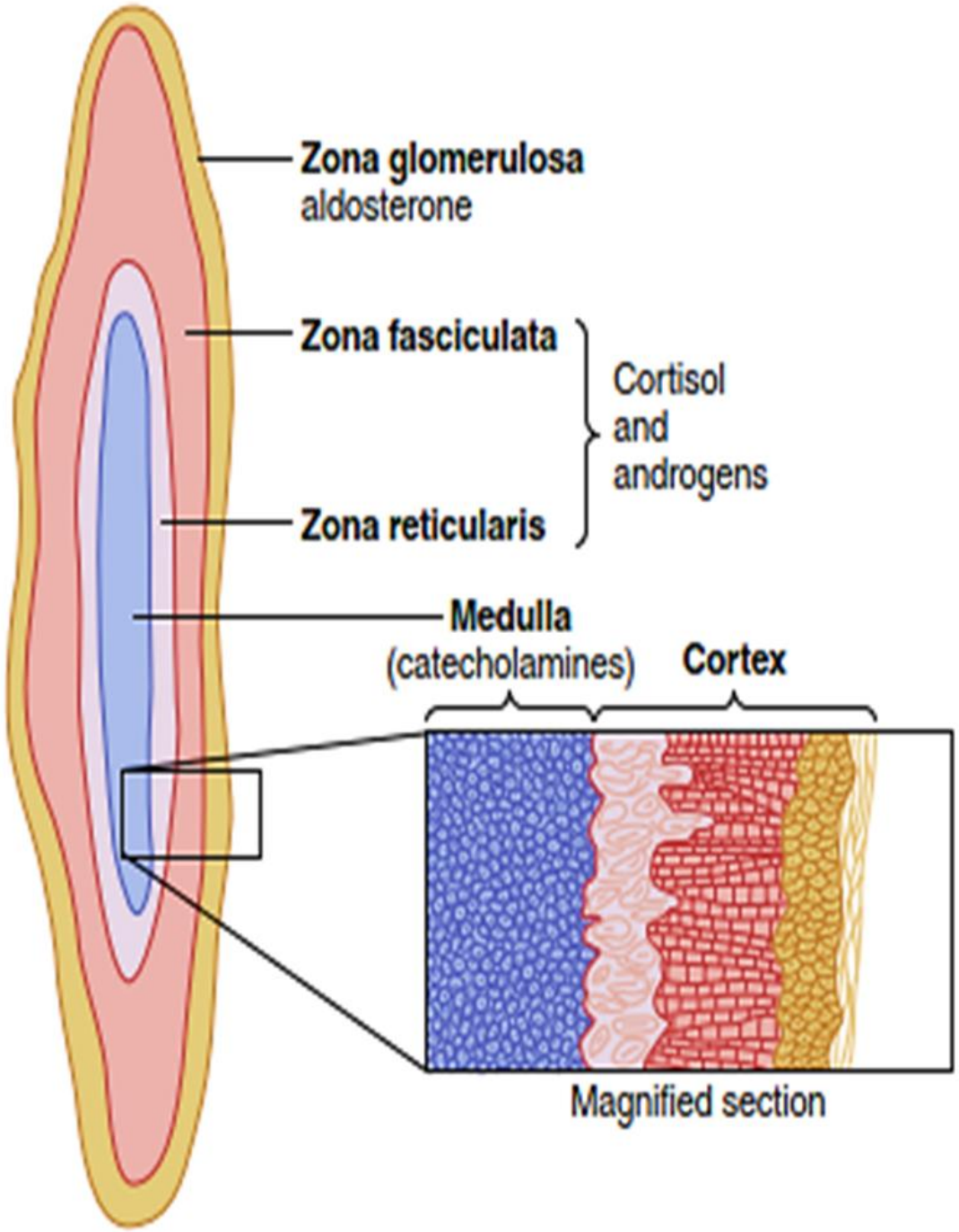
Adrenal cortex. The adrenal cortex forms the outer portion of the adrenal gland and accounts for 80 to 90% of the weight of the gland.

The zona glomerulosa is the outermost layer of the adrenal cortex, and is responsible for secreting the **mineralocorticoid** hormones,such as aldosterone, which are important in regulating fluid and electrolyte balance.
The middle layer of the adrenal cortex is the **zona fasciculata**.

It is the thickest of the three Zonas, measuring approximately

0.9mm and making up 50% of the mass of the Adrenal Gland. The cells of the zona fasciculata secrete the **glucocorticoids** cortisol and corticosterone, which regulate carbohydrate metabolism in the body.

The zona reticularis is the innermost layer of the adrenal cortex. It is responsible for production and secretion of **androgens**, these are responsible for the normal development of sexual characteristics during puberty



Mineralocorticoids
Glucocorticoids
Adrenal androgens

Mineralocorticoids. The primary mineralocorticoid is *aldosterone*. The actions of this hormone include:

- **Stimulation of renal retention of sodium**
- **Promotion of renal excretion of potassium**

Aldosterone acts on the distal tubule of the nephron to increase sodium reabsorption. Due to its osmotic effects, the retention of sodium is accompanied by the retention of water. As a result, aldosterone is very important in regulation of blood volume and blood pressure. The retention of sodium and water expands the blood volume and, consequently, increases mean arterial pressure. The retention of sodium is coupled to the excretion of potassium. For every three Na^+ ions reabsorbed, two K^+ ions and one H^+ ion are excreted.

The release of aldosterone from the adrenal cortex is regulated by two important factors:

- **Serum potassium levels**
- **The renin–angiotensin system**

An increase in the level of potassium in the blood stimulates the release of aldosterone. The effect of aldosterone on the kidney then decreases the level of potassium back to normal.

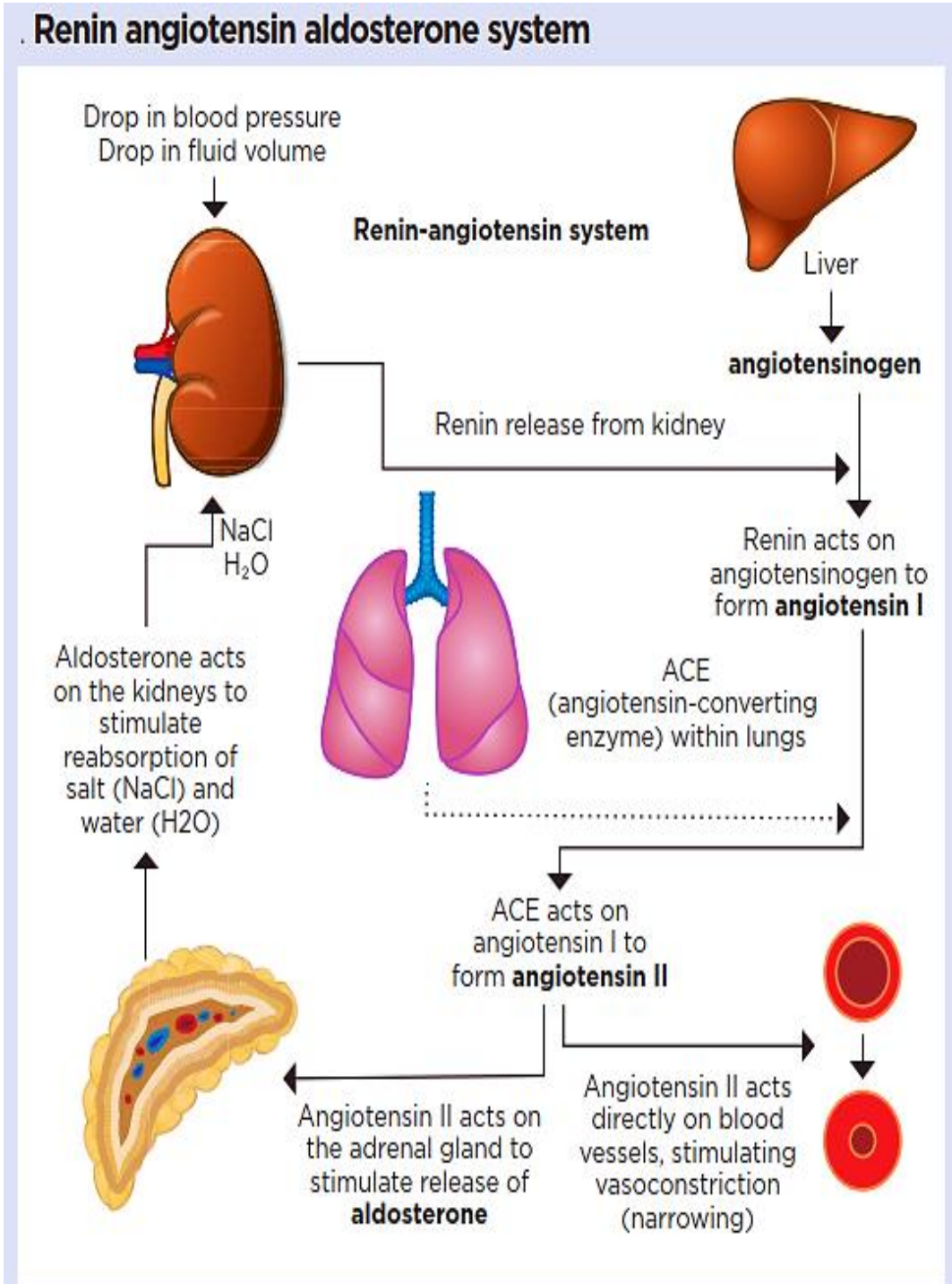
Angiotensin II (Ag II) is a potent stimulus for the secretion of aldosterone. **Angiotensinogen** is a precursor peptide molecule released into the circulation from the liver. In the presence of **renin**, an enzyme produced by specialized cells in the kidney, angiotensinogen is split to form **angiotensin I**. This prohormone is then acted upon by **angiotensin-converting enzyme (ACE)** as the blood passes through the lungs to form **Ag II**. Angiotensin II acts directly on the adrenal cortex to promote aldosterone secretion.

Because this process requires renin in order to occur, it is important to understand the factors involved in its release from the kidney. These factors include:

Decrease in blood volume
Decrease in blood pressure
Sympathetic stimulation

A decrease in blood volume or blood pressure may result in a decrease in the blood flow to the kidney. The kidney monitors renal blood flow by way of stretch receptors in the vessel walls. A decrease in renal blood flow stimulates the release of renin. The subsequent secretion of aldosterone causes retention of sodium and water and, therefore, an increase in blood volume and blood pressure back to normal. An increase in renal blood flow tends to cause the opposite effect.

Activation of the sympathetic system also promotes renin release.



Glucocorticoids. The primary glucocorticoid is ***cortisol***. Receptors for the glucocorticoids are found in all tissues. The overall effects of these hormones include:

Increase in blood glucose
Increase in blood free fatty acids

Cortisol increases blood glucose by several mechanisms of action including:

Decrease in glucose utilization by many peripheral tissues (especially muscle and adipose tissue)

Increase in availability of gluconeogenic substrates

Increase in protein catabolism (especially muscle)

Increase in lipolysis

Increase in hepatic gluconeogenesis

Cortisol-induced lipolysis not only provides substrates for gluconeogenesis (formation of glucose from noncarbohydrate sources) but it also increases the amount of free fatty acids in the blood. As a result, the fatty acids are used by muscle as a source of energy and glucose is spared for the brain to use to form energy.

On minerals, it has a similar effect to aldosterone, although it is weaker than it (1/10 the power of Aldosterone). It promotes sodium retention and potassium elimination, excessive secretion will lead to more sodium retention → water retention

The release of cortisol from the adrenal cortex is regulated by several factors including:

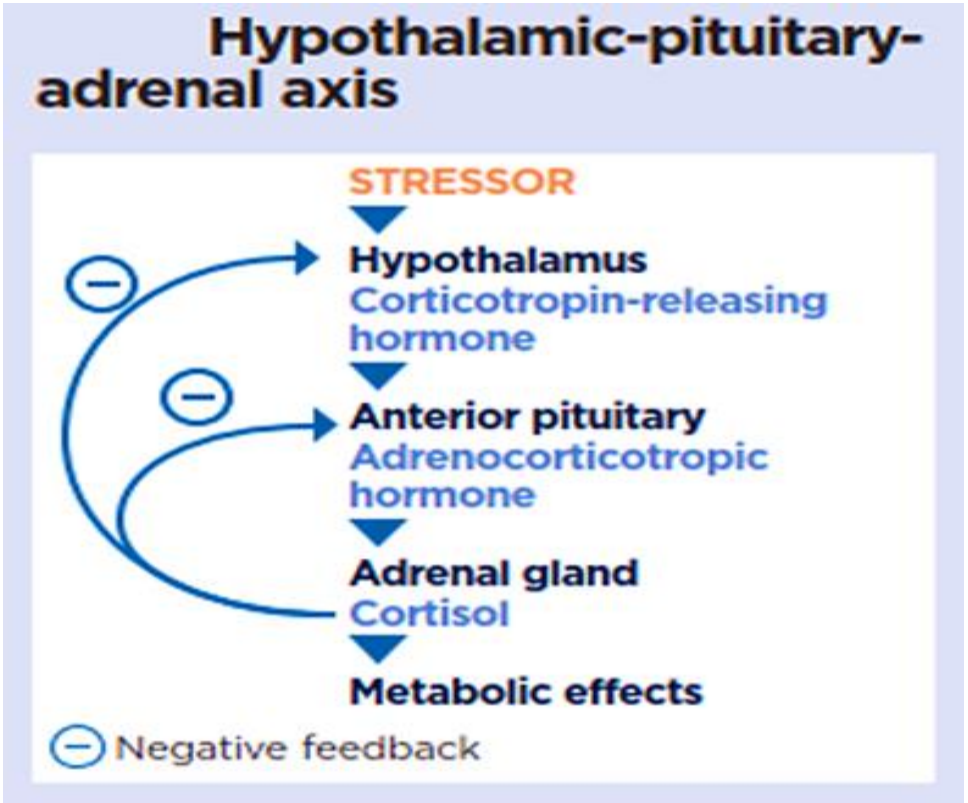
Circadian rhythm
Stress
Negative-feedback inhibition by cortisol

Corticotropin-releasing hormone (CRH) secreted from the hypothalamus stimulates the release of ACTH from the adenohypophysis. This pituitary hormone then stimulates the release of cortisol from the adrenal cortex. The hormones of this hypothalamic–pituitary–adrenocortical axis exhibit marked diurnal variation. This variation is due to the diurnal secretion of CRH. The resulting secretion of ACTH increases at night and peaks in the early morning just before rising (4 A.M. to 8 A.M.). The levels of ACTH then gradually fall during the day to a low point late in the evening, between 12 P.M. and 4 P.M. This rhythm is influenced by many factors, including light–dark patterns, sleep–wake patterns, and eating. After an individual changes time zones, it takes about 2 weeks for this rhythm to adjust to the new time schedule; this may account for some aspects of jet lag.

Cortisol is an important component of the body's response to physical and psychological stress. Nervous signals regarding stress are transmitted to the hypothalamus and the release of CRH is stimulated.

The resulting increase in cortisol increases levels of glucose, free fatty acids, and amino acids in the blood, providing the metabolic fuels that enable the individual to cope with the stress.

A potent inhibitor of this system is cortisol itself. This hormone exerts a negative-feedback effect on the hypothalamus and the adenohypophysis and inhibits the secretion of CRH and ACTH, respectively.



Therapeutic effects of corticosteroids

When administered in pharmacological concentrations (greater than physiological), cortisol and its synthetic analogs (hydrocortisone, prednisone) have potent **anti-inflammatory** and **immunosuppressive** effects. In fact, these steroids inhibit almost every step of the inflammatory response resulting in the decreased release of vasoactive factors, decreased secretion of lipolytic and proteolytic enzymes, decreased extravasation of leukocytes to areas of injury, and, ultimately, decreased fibrosis.

Typically, the inflammatory response is quite beneficial in that it limits the spread of infection. However, in many clinical conditions, such as rheumatoid arthritis and asthma, the response becomes a destructive process. Therefore, although glucocorticoids have no effect on the underlying cause of disease, the suppression of inflammation by these agents is very important clinically.

Corticosteroids also exert inhibitory effects on the overall immune process. These drugs impair the function of the leukocytes responsible for antibody production and destruction of foreign cells. As a result, corticosteroids are also used therapeutically in the prevention of organ transplant rejection.

Effect on respiration:

It is important for the synthesis of surfactant during intrauterine life (to prevent respiratory distress syndrome). In females who are about to deliver preterm babies we usually give them cortisol to promote the formation of surfactant.

Effect on water balance:

It causes sodium retention which leads to water retention .It also causes increase in GFR (glomerular filtration rate), which counteract the water retention and the person does not develop edema.

Effect on cardiovascular system:

Cortisol restores vascular reactivity. It helps in maintaining arterial response to sympathetic tone. Deficiency of the hormone leads to hypotensive subject due to failure to maintain the peripheral resistance. While patients with hyper function of the adrenal cortex are hypertensive (because of the increase in peripheral resistance).

Effect on GIT:

Cortisol reduces the resistance of gastric mucosa to HCL so increase secretion of it leads to ulcer (so before giving the patient steroid tablets ask him if he has gastric pain or ulcer otherwise it may cause perforation to the stomach). Also it has an antivitamin D effect .It prevent the absorption of the vitamin from the intestine.

Effect on lymphoid tissue and heamopoiesis:

Cortisol suppresses the **production of antibodies** (used in chronic inflammatory diseases) in which inappropriate antibodies are produced in the subject against his own tissues (The administration of large doses of cortisol causes decreases the output of both T cells and antibodies from the lymphoid tissue. **As a result, the level of immunity for almost all foreign invaders of the body is decreased**. Conversely, this ability of cortisol and other glucocorticoids to suppress immunity makes them useful drugs in preventing immunological rejection of transplanted hearts, kidneys, and other tissues.

Effect on bones:

Excessive secretion leads to osteoporosis due to destruction of the matrix of the bone (catabolic effect of cortisol on protein found in the matrix).This effect of cortisol in mobilizing proteins could make amino acids available to needs of the cells to synthesize substances essential to life.

Anti- inflammatory effect of cortisol: It has the following effects to prevent inflammation:

*1-**Cortisol stabilizes the lysosomal membranes***, so decreases the proteolytic enzymes that are released by the lysosomes**.**

2.Cortisol decreases the permeability of the capillaries. This prevents loss of plasma into the tissues.

3.Cortisol decreases both migration of white blood cells *into the inflamed area and* ***phagocytosis*** *of the damaged cells.*

4.Cortisol suppresses the immune system*, causing lymphocyte reproduction todecrease markedly(especially T lymphocytes).*

*5.**Cortisol attenuates fever*** *mainly because it reduces the release of interleukin-1 from the white blood cells.*

In addition to that Cortisol causes resolution of inflammation, the rate of healing is enhanced. So it can be used in disease that are characterized by severe local inflammation like rheumatoid arthritis, rheumatic fever, and acute glomerulonephritis.

Effect on allergy:

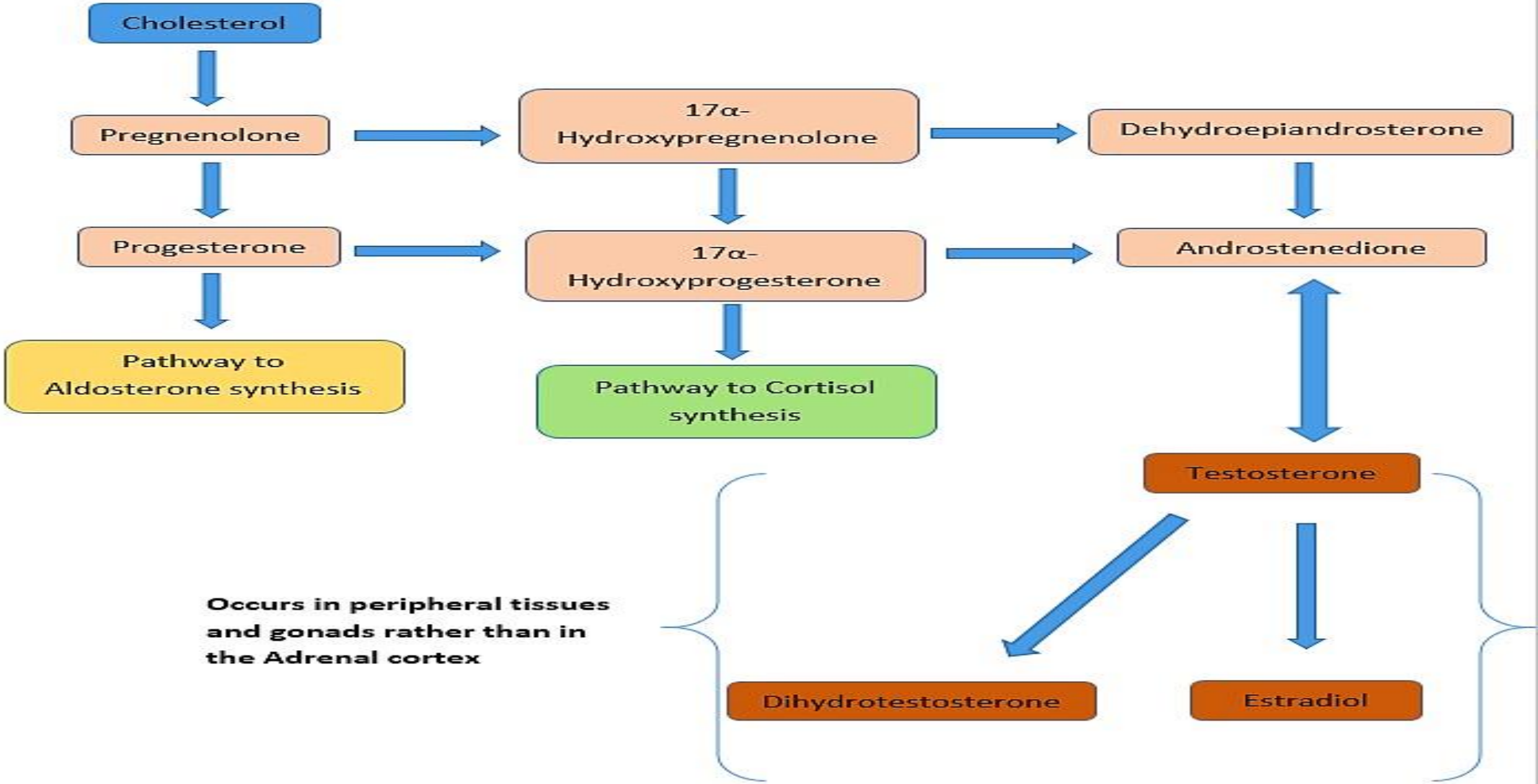
It blocks the inflammatory response to allergic reactions in the same way that it blocks the other types of inflammatory response.

Effect on blood:

It decreases the number of eosinophils and lymphocytes in the blood. It also increases the production of red blood cells (mechanisms unclear).When excess cortisol is secreted by the adrenal glands, polycythemia often results, and conversely, when the adrenal glands secrete no cortisol, anemia often results.

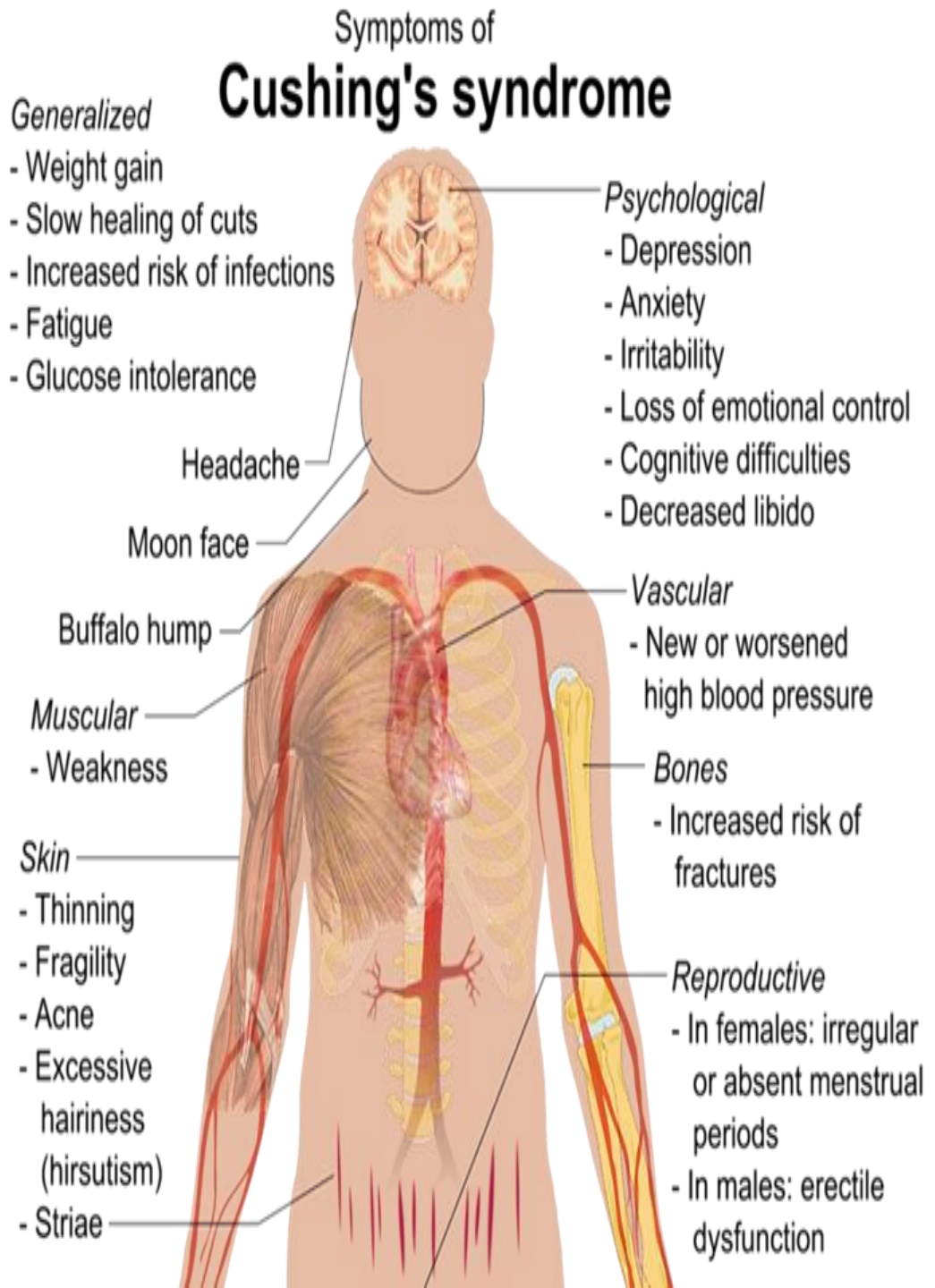
The synthesis pathway of the steroids secreted by the Zonas of the adrenal gland is complex. **Cholesterol** is the major precursor for all steroids secreted. The first step is initiated by the actions of ACTH and Angiotensin II activating **adenylyl cyclase** and **phospholipase C** respectively. Cholesterol can then be converted to a steroid called Pregnenolone via an enzyme of the cytochrome P450 superfamily called cholesterol desmolase. From Pregnenolone, all the major secreted **mineralocorticoids,** glucocorticoids and androgens can be synthesised in a multi-step enzyme-assisted pathway. The metabolites of the synthesis pathway are moved in and out of the mitochondria, the smooth endoplasmic reticulum and the cytoplasm. It is the presence or lack of specific enzymes in each Zona that determines which hormones are secreted. In the Zona Fasciculata, the enzyme **11β-hydroxylase** catalyses the final step of the reaction that forms Cortisol and Corticosterone. Additionally the secretion of cortisol follows a **diurnal pattern** with more being secreted in the mornings.

Synthesis of Hormones in Adrenal Cortex



Cushing’s Syndrome

In a steroid-producing adrenal tumour (or Anterior Pituitary adenoma), large concentrations of **glucocorticoids** are secreted in the body. When in high concentrations, glucocorticoid steroids activate mineralacorticoid receptors due to the similarity in shape of the receptors. Therefore, a patient with Cushing’s Syndrome will have symptoms of high **glucocorticoid** secretion (fat build-up on back of neck and around face, wasting of limb muscles with central obesity, purple striae, hyperpigmentation) as well as show effects of high **mineralocorticoid** concentrations (hypertension, hypokalaemia). Treatment of Cushing’s depends on the underlying cause, for example a **pituitary adenoma** may be surgically removed, as can a metastatic lung tumour secreting ACTH.



Addison's disease : is the opposite disease to Cushing's disease in many ways. Whereas Cushing's disease is due to an excess of cortisol, Addison's disease is due to a lack of cortisol, commonly due to autoimmune destruction of the adrenal cortex. This in turn causes hypotension and anorexia, in contrast to hypertension and truncal obesity in Cushing's disease. A unique symptom of Addison's disease is hyperpigmentation, particularly in the creases of the hand and in the mouth. A very serious complication of Addison's disease is an Addisonian crisis. As discussed above, cortisol is linked to the "fight or flight" response and is released in times of stress to the body. Therefore, in patients suffering from Addison's disease, they are unable to mount an adequate response to these stresses. This can result in numerous symptoms such as severe hypotension and electrolyte dysfunction.

Regulation of Adrenal Androgens

Adrenal androgens are regulated by ACTH (adrenocorticotropic hormone) secreted from the anterior pituitary gland which is stimulated by the release of CRH (corticotrophin releasing hormone) from the **hypothalamus.** However, the adrenal androgens along with their potent metabolites such as testosterone do not negatively feedback to ACTH or CRH. Therefore, in cases where there is a dramatic increase in ACTH, this leads to excess production of androgens which cannot be regulated.

Parathyroid Hormone, Calcitonin, Calcium and Phosphate Metabolism, Vitamin D

CALCIUM AND PHOSPHATE REGULATION IN EXTRACELLULAR FLUID AND PLASMA

- Extracellular fluid calcium concentration is normally regulated precisely; it seldom rises or falls more than a few percent from the normal value of about **9.4 mg/dl, which is equivalent to 2.4 millimoles of calcium per liter**. This precise control is essential because calcium plays a key role in many physiological processes, including contraction of skeletal, cardiac, and smooth muscles, blood cloting, and transmission of nerve impulses.

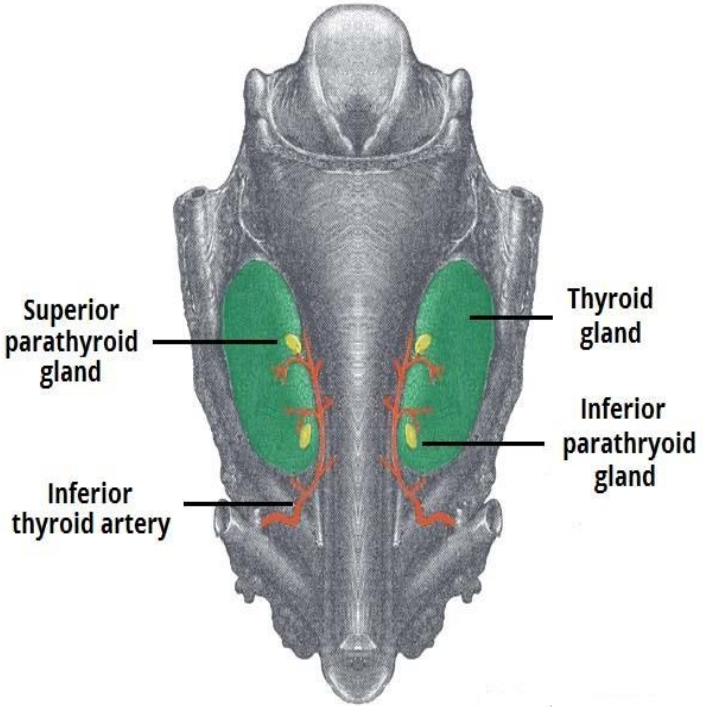
- Excitable cells such as neurons are sensitive to changes in calcium ion concentrations, and increases above normal (hypercalcemia) cause progressive depression of the nervous system; conversely, decreases in calcium concentration (hypocalcemia) cause the nervous system to become more excited.
- An important feature of extracellular **calcium** regulation is that only about 0.1% of the total body calcium is in the extracellular fluid, about 1% is in the cells and its organelles, and the rest is stored in bones. Therefore, the bones can serve as large reservoirs, storing excess calcium and releasing calcium when extracellular fluid concentration decreases.
- Approximately 85% of the body's **phosphate** is stored in bones, 14% to 15% is in the cells, and less than 1% is in the extracellular fluid.

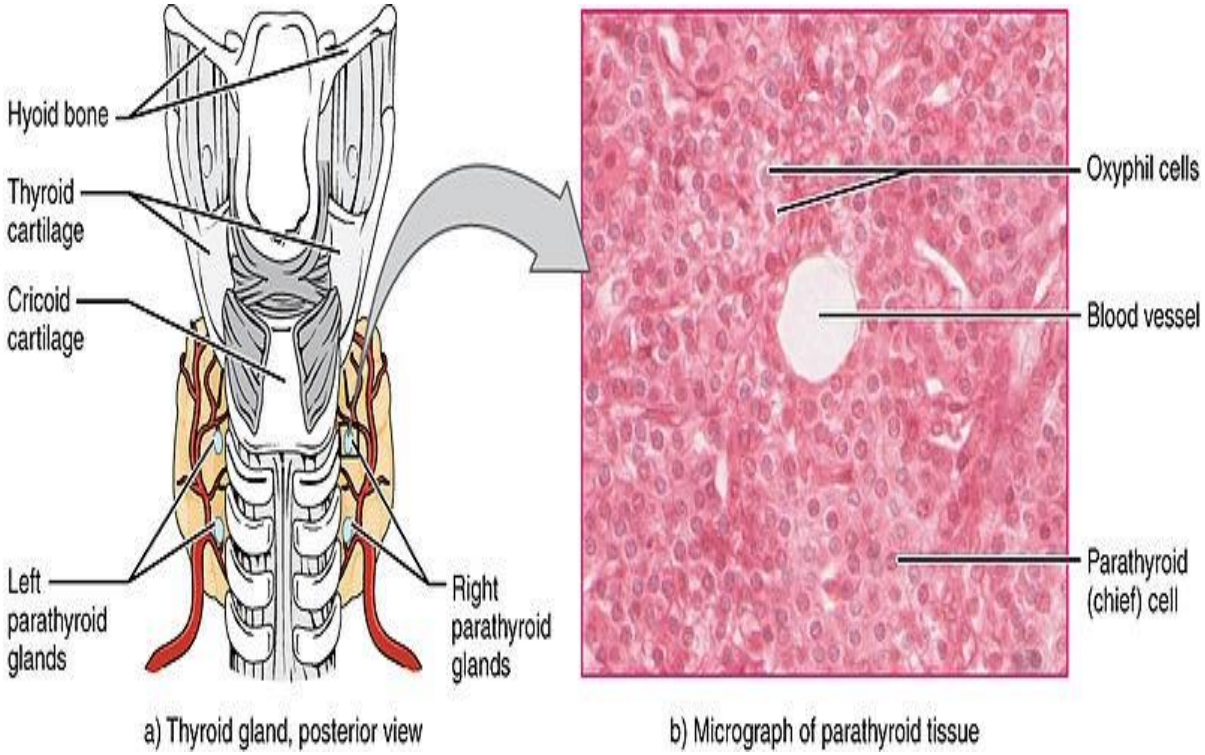
The parathyroid glands

- are small endocrine glands located in the anterior neck. They are responsible for the production of parathyroid hormone (PTH). The parathyroid glands are located on the posterior, medial aspect of each lobe of the thyroid gland. Anatomically, the glands can be divided into two pairs:
- Superior parathyroid glands – Derived embryologically from the fourth pharyngeal pouch. They are usually located at the level of the inferior border of the cricoid cartilage.
- Inferior parathyroid glands – Derived embryologically from the third pharyngeal pouch. They are usually located near the inferior poles of the thyroid gland. However in 1-5% of people they can be found deep in the superior mediastinum.
- Parathyroid Gland Histology : There are two types of cells within the parathyroid gland, the chief cells and the oxyphil cells.
- Chief cells– The role of this cell type is to secrete parathyroid hormone. They contain prominent Golgi apparatus and endoplasmic reticulum to allow for the synthesis and secretion of parathyroid hormone. The chief cells are the smaller of the two cell types, however, they are more abundant. Oxyphil cells– These cells are much larger but less abundant than chief cells. Their purpose is unknown.Note that histologically fat cells (adipose cells) are also seen within the parathyroid gland.

The parathyroid glands

- **Anatomical location of the parathyroid gland and their histology.**





a) Thyroid gland, posterior view

b) Micrograph of parathyroid tissue

The parathyroid glands

Parathyroid Hormone Actions

Parathyroid hormone (PTH) has three main actions, all of which act to increase calcium levels in the body;

Increased bone resorption– PTH acts directly on bone to increase bone resorption. It induces cytokine secretion from osteoblasts that act on osteoclast cells to increase their activity. Osteoclasts are responsible for the breakdown of bone and thus an increase in their activity leads to increased bone break down. This leads to an increase in calcium in the extracellular fluid.

Increased reabsorption in the kidney- PTH increases the amount of calcium absorbed from the Loop of Henle and distal tubules, however, the mechanism is not fully understood. Additionally, PTH increases the rate of phosphate excretion which is very important to prevent the formation of calcium phosphate kidney stones.

Vitamin D synthesis- Although PTH does not actively increase the absorption of calcium from the gut it stimulates the formation of vitamin D, which subsequently increases absorption from the gut.

The parathyroid glands

Parathyroid Hormone Regulation

Like most endocrine organs, the parathyroid gland is controlled by a **negative feedback loop**. Chief cells have a unique G-protein calcium receptor (CaR) on their surface, which regulates this. When **calcium levels** in the blood are elevated, PTH production must be stopped in order to prevent further elevation of calcium which could lead to hypercalcaemia. Calcium binds to the G protein CaR which subsequently leads to the prevention of PTH secretion thus calcium is deposited back into the bones.

Furthermore, as mentioned above, PTH stimulates **vitamin D** synthesis. Vitamin D also acts directly on the parathyroid gland to decrease PTH synthesis.

When Calcium is reduced, the reverse occurs. Lowered calcium means reduced stimulation of CaR. Subsequently, PTH secretion is not inhibited. Decreased Vitamin D results in upregulation of PTH gene transcription thus more PTH is synthesised.

Note: Elevated phosphate lowers free Calcium in the blood and inhibits the formation of Vitamin D.

The parathyroid glands

Clinical Relevance – Hyperparathyroidism

Hyperparathyroidism is the over-activity of the parathyroid glands and can be classed as primary, secondary, tertiary or malignant depending on the underlying cause.

Primary hyperparathyroidism is a result of direct alterations to the parathyroid gland such as a benign tumour, hyperplasia or very rarely parathyroid cancer. The excess secretion of PTH leads to elevated calcium in the blood which can cause signs of hypercalcaemia, osteoporosis, osteitis fibrosa cystica and hypertension.

Secondary hyperparathyroidism is a physiologically elevated PTH due to reduced calcium levels. This could be caused by chronic renal failure or decreased vitamin D intake.

Tertiary hyperparathyroidism occurs after prolonged secondary hyperparathyroidism. This is due to structural changes seen within the gland.

Malignant hyperparathyroidism can be caused by some tumours, such as bronchial squamous cell carcinomas, as they produce a protein called Parathyroid related protein (PTHrP). PTHrP can mimic PTH due to the similarity in their structure which ultimately results in elevated calcium in the blood. However, PTH will be reduced due to negative feedback to the parathyroid gland itself.

The parathyroid glands

Hypoparathyroidism

Hypoparathyroidism is the underactivity of the parathyroid gland and can be classed as primary or secondary depending on the cause.

Primary hypoparathyroidism is a result of decreased PTH secretion due to gland failure. This results in symptoms of hypocalcaemia and patients will often need Calcium supplementation.

Secondary hypoparathyroidism is commonly caused by surgical removal of the parathyroid glands. This is often accidental due to the fact that the inferior parathyroid glands are difficult to locate.

Calcitonin

It is a peptide hormone secreted by the thyroid gland , it decreases plasma calcium concentration &has effects opposite to those of PTH . Synthesis & secretion of calcitonin occur in the Para follicular cells or C cells , lying in the interstitial fluid between the follicles of the thyroid gland .The primary stimulus for calcitonin secretion is increased calcium ion concentration in plasma .

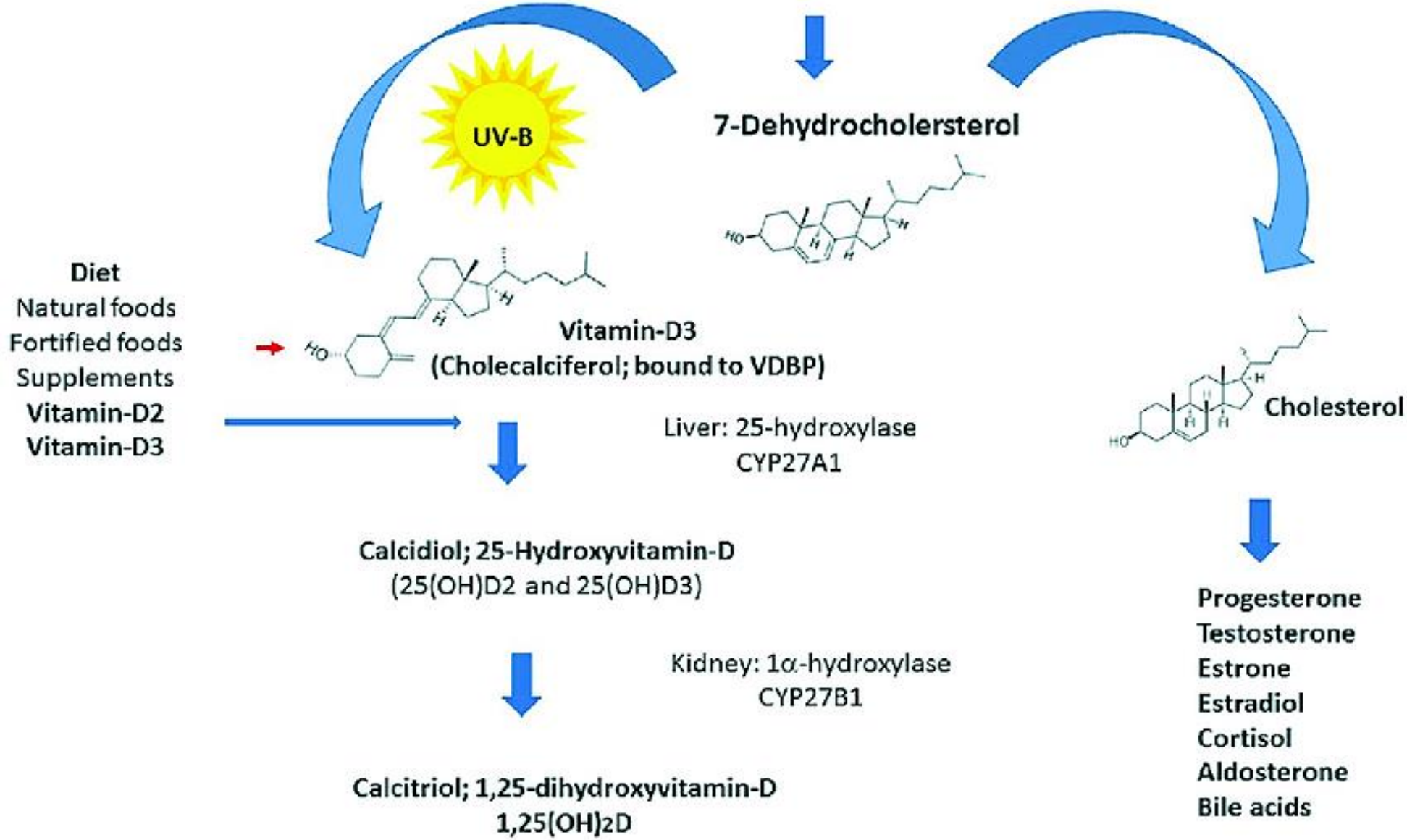
Vitamin D

Vitamin D is a long-term regulator of serum calcium, with a half life of around 6 hours. Its main function is to increase the intestinal absorption of calcium.

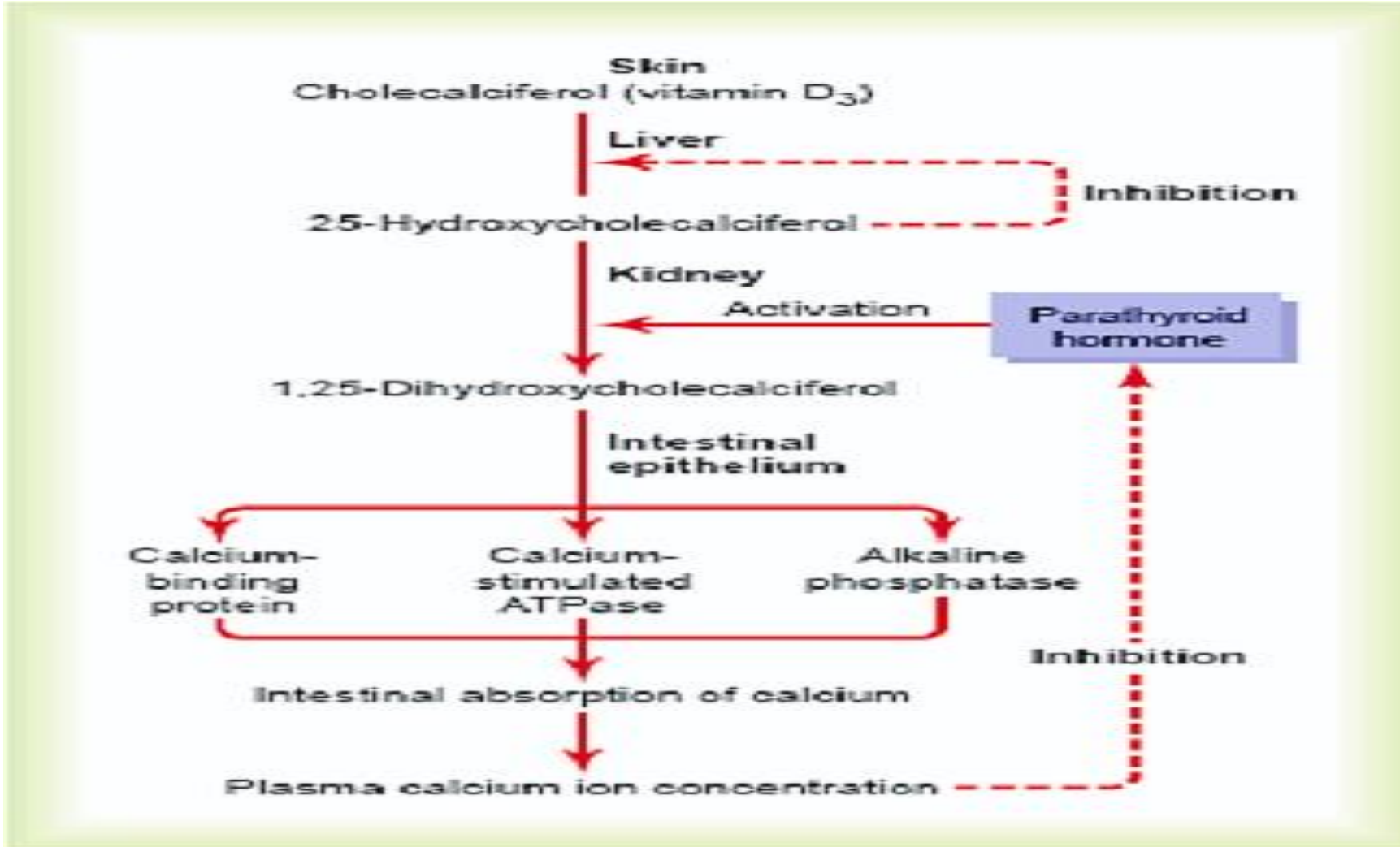
Vitamin D3 (cholecalciferol) is found in the skin .This is activated &converted to 25-hydroxycholecalciferol in the liver & this has a negative feedback effect on the conversion reactions.

25-hydroxycholecalciferol in the proximal tubules of the kidneys is converted to 1, 25-dihydroxycholecalciferol .this is the most active form of vitamin D .this conversion requires PTH .

So it can be ingested, or synthesized from a cholesterol precursor as follows:
7-dehydrocholesterol is converted into vitamin-D3 under the influence of UV radiation.
In the liver, vitamin-D3 is converted into 25-hydroxyvitamin-D.This is relatively inactive. In the kidney, conversion of 25-hydroxyvitamin-D into 1,25-dihydroxyvitamin-D, otherwise known as calcitriol. This is metabolically active.
Once synthesized, calcitriol is released into the bloodstream. It then stimulates intestinal epithelial cells to increase absorption of calcium.
If levels of calcitriol become excessive, it is converted to 24,25-dihydroxycholecalciferiol, which is less active. This prevents toxicity.



Schematic diagram of Vitamin D synthesis



Activation of vitamin D_3 to form 1,25-dihydroxycholecalcifero and the role of vitamin D in controlling the plasma calcium concentration.

Actions of vitamin D

1. It promotes intestinal calcium absorption .
2. It promotes phosphate absorption by the intestines .
3. It decreases renal calcium and phosphate excretion .
4. It plays an important role in both bone absorption & bone deposition .

Calcium & phosphate regulation in the extra cellular fluid & plasma

Calcium plays a key role in many physiological processes including :

Contraction of skeletal ,cardiac and smooth muscle , Blood clotting , Transmission of nerve impulses . Only 0.1% of total body Ca is in the ECF , 1% is in the cells and the rest is stored in the bones.

About 85% of the body s phosphate is stored in bones , 14 – 15 %is in the cells and less than 1% is in the ECF. Calcium in the blood exists in three forms:

Free-ionised – diffusible, biologically active.

Bound to anions e.g. phosphate – diffusible, not biologically active.

Bound to proteins (mainly albumin) – not diffusible, not biologically active.

Non –bone physiologic effect of altered Ca & phosphate concentrations in the body fluids.

Hypocalcemia causes nervous system excitement & tetany .Hypercalcemia decreases nervous system & muscle activity. When ECF concentration of Ca ions falls below normal the nervous system becomes more excitable , because this causes increased neural membrane permeability to Na ions allowing easy initiation of action potential .

At plasma Ca 50% below normal , the peripheral nerve fibers become so excitable that they discharge spontaneously initiating nerve impulses that pass to the peripheral skeletal muscles to cause tetanic muscle contraction .It also causes seizures because of its action of increasing excitability of the brain. this pic. Shows carpopedal spasm.

Tetany occurs when the blood concentration of Ca falls from 9.4 mg / dl to about 6 mg / dl , which is only 35% below normal & is usually lethal at about 4 mg / dl .

When calcium level in the body fluids rises above normal , the nervous system becomes depressed & reflex activities of the nervous system are sluggish , also decrease the QT interval of the heart ECG , constipation and lack of appetite.

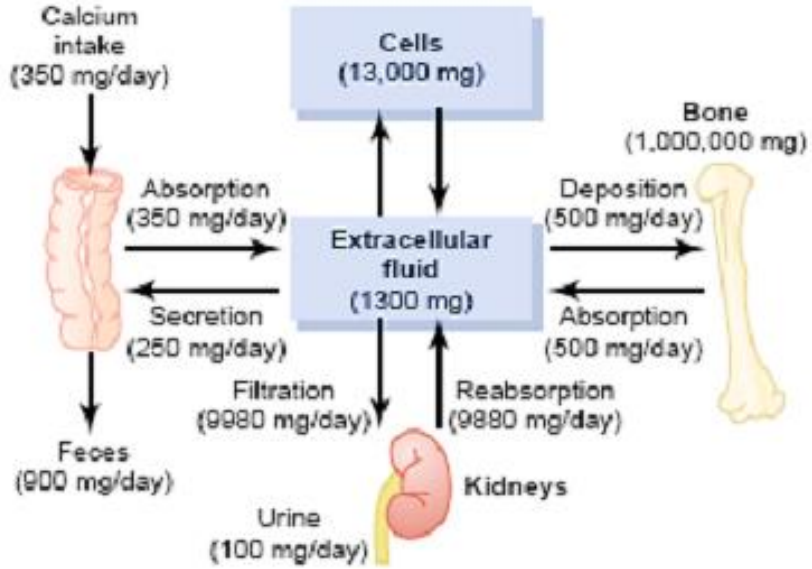
These effects occur when the level of calcium rises above 12 mg / dl, when the level of calcium rises above 17mg /dl in blood , calcium , phosphate crystals precipitate throughout the body.

Hypocalcemic tetany in the hand, called carpopedal spasm.

Absorption & excretion of calcium and phosphate

Intestinal absorption & fecal excretion : the usual rates of intake are about 1000 mg / day for calcium & phosphate , Ca ions are poorly absorbed from the intestine , vitamin D promotes its absorption by the intestine. about 35%(350 mg / day) of ingested calcium is usually absorbed , the remaining is excreted in the feces, an additional 250 mg of calcium enters the intestine via secreted G.I.T. juices thus 90% (900 mg / day) of daily intake of calcium is excreted in feces.

Intestinal absorption of phosphate occurs very easily. Except for the portion of phosphate that is excreted in the feces in combination with non-absorbed calcium, almost all the dietary phosphate is absorbed into the blood from the gut and later excreted in the urine.



Overview of calcium exchange between different tissue compartments in a person ingesting 1000 mg of calcium per day. Note that most of the ingested calcium is normally eliminated in the feces, although the kidneys have the capacity to excrete large amounts by reducing tubular reabsorption of calcium.

Renal excretion of calcium & phosphate

About 10% (100 mg / day) of ingested calcium is excreted in urine . About 41%of plasma calcium is bound to plasma proteins and therefore not filtered by the glomerular capillaries . The rest is combined with anions such as phosphate (9%) or ionized 50% and is filtered through the glomeruli into the renal tubules .

Normally renal tubules absorb 99% of the filtered calcium & about 100mg / day is excreted in urine . About 90%of calcium in the glomerular filtrate is reabsorbed in the proximal tubules , loop of Henle and early distal tubules , then in the late distal tubular and early collecting ducts ,reabsorption of remaining 10% is very selective , depending on calcium ion concentration in blood .

When concentration is low , this reabsorption is great , so that almost , no calcium is lost in urine . Conversely , even a minute increase in blood calcium ion concentration above normal increases excretion markedly.

Renal phosphate excretion is controlled by an overflow mechanism that is when phosphate concentration in the plasma is below the critical value of about 1 mmol / L, all the phosphate in the glomerular filtrate is reabsorbed & no phosphate is lost in the urine .

Regulation

There are three molecules which regulate the amount of calcium in blood and ensure it is maintained within the normal range. These are calcitriol (vitamin D), parathyroid hormone and calcitonin. The synthesis of calcitriol is completed in the kidneys, parathyroid hormone (PTH) is secreted by the parathyroid glands, and calcitonin is secreted by the thyroid glands.

Clinical Relevance : Hypocalcaemia

Hypocalcaemia is defined as an adjusted calcium level of <2.20mmol/L.

Patients who develop hypocalcaemia acutely tend to be more symptomatic compared to patients who develop hypocalcaemia over a long period of time (chronic hypocalcaemia).

The symptoms of hypocalcaemia include peri-oral and peripheral numbness or tingling, cardiac arrythmias (prolonged QT interval on ECG), muscle spasms, and seizures. This is due to a reduction in the resting membrane potential, rendering the cell hyper-excitable.

Causes of hypocalcaemia include:

- Hypoparathyroidism
- Vitamin D deficiency
- Hyperphosphatemia: Phosphate binds to calcium to form calcium phosphate, reducing free calcium.
- Renal disease: Reduced calcitriol synthesis.
- Acute pancreatitis: Free fatty acids bind calcium, reducing levels of free calcium.
- Respiratory alkalosis: In alkalosis, calcium ions associate with albumin with greater affinity, thus reducing free and active calcium.

Hypercalcaemia

Hypercalcaemia is defined as an adjusted calcium level of >2.60mmol/L.
Patients with mild hypercalcemia tend to be asymptomatic, but when levels exceed 3mmol/L, symptoms include muscle weakness, cardiac arrhythmias (short QT interval), constipation, kidney stones and depression.

Causes of hypercalcaemia include:

- Hyperparathyroidism
- Malignant tumour – Some tumours secrete parathyroid-hormone related peptide (PTHrP). This mimics PTH, leading to hypercalcaemia.
- Vitamin D intoxication – excess vitamin D causing increased intestinal absorption of calcium.
- Thiazide diuretics – increase renal reabsorption of calcium causing excess calcium in blood.


Thank you.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