

Minerals

Of the large number of minerals present in nature, only a few are essential for human beings

Some of these are required in relatively large quantities, and are known as principal elements or macronutrients

These include calcium, phosphorus, magnesium, sodium, potassium, chlorine and sulphur

Some minerals are required in minute quantities, and are known as trace elements or micro-nutrients

These include iron, iodine, copper, zinc, cobalt, manganese, molybdenum, chromium, selenium and fluorine

Calcium

Calcium is the most abundant mineral in human beings

Total calcium in an average adult is about 1,000 gm of which nearly 99% is present in bones and teeth

The rest (about 10 gm) is distributed in various tissues and body fluids

1 Muscles and nerves have relatively more calcium than other tissues

2 Calcium is present in bones mainly in the form of calcium phosphate

3 Small amounts of carbonate, hydroxide, fluoride, citrate and other salts of calcium are also present

Calcium phosphate is first deposited in an amorphous form which is later converted into crystalline form

The crystalline form is known as hydroxyapatite, and its rough composition is $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$

The crystals are rod-shaped

There is a continuous exchange of calcium

Concentration of calcium in intracellular and extracellular fluids is delicately regulated

The concentration of calcium in plasma (or serum) is 9-11 mg/dl (4.5-5.5 mEq/L)

About 50% of this is bound to proteins, and can not diffuse through capillaries (protein-bound or non-diffusible calcium)

- About 5% is associated with organic anions e.g. citrate, and is diffusible
- The remaining 45% is free ionized calcium, and is freely diffusible
- Almost all the physiological functions of calcium are performed by ionized calcium

• **Functions**

- Formation of bones and teeth
- Excitability and conductivity of nerves
- Neuromuscular transmission
- Excitability and contractility of myocardium
- Coagulation of blood
- Action of hormones

Formation of bones and teeth

A major function of calcium is to form bones and teeth

Calcium phosphate is deposited around collagen fibres in the zone of ossification

It is first deposited in an amorphous form which changes later into hydroxyapatite crystals

Osteoblasts mineralize the bones and osteoclasts remove minerals from the bones

In growing age, osteoblastic activity is more than the osteoclastic activity leading to skeletal growth

In adults, the activities are balanced leading to a continuous remodelling of the bones

Excitability and conductivity of nerves

- Excitability of nerves depends upon a number of cations including Ca^{++}
- A raised plasma Ca^{++} level decreases, and a lowered plasma Ca^{++} level increases the excitability of nerves
- Transmission of impulses across synapses occurs due to release of neurotransmitters which requires

Neurotransmitters are present in the cell inside synaptic vesicles

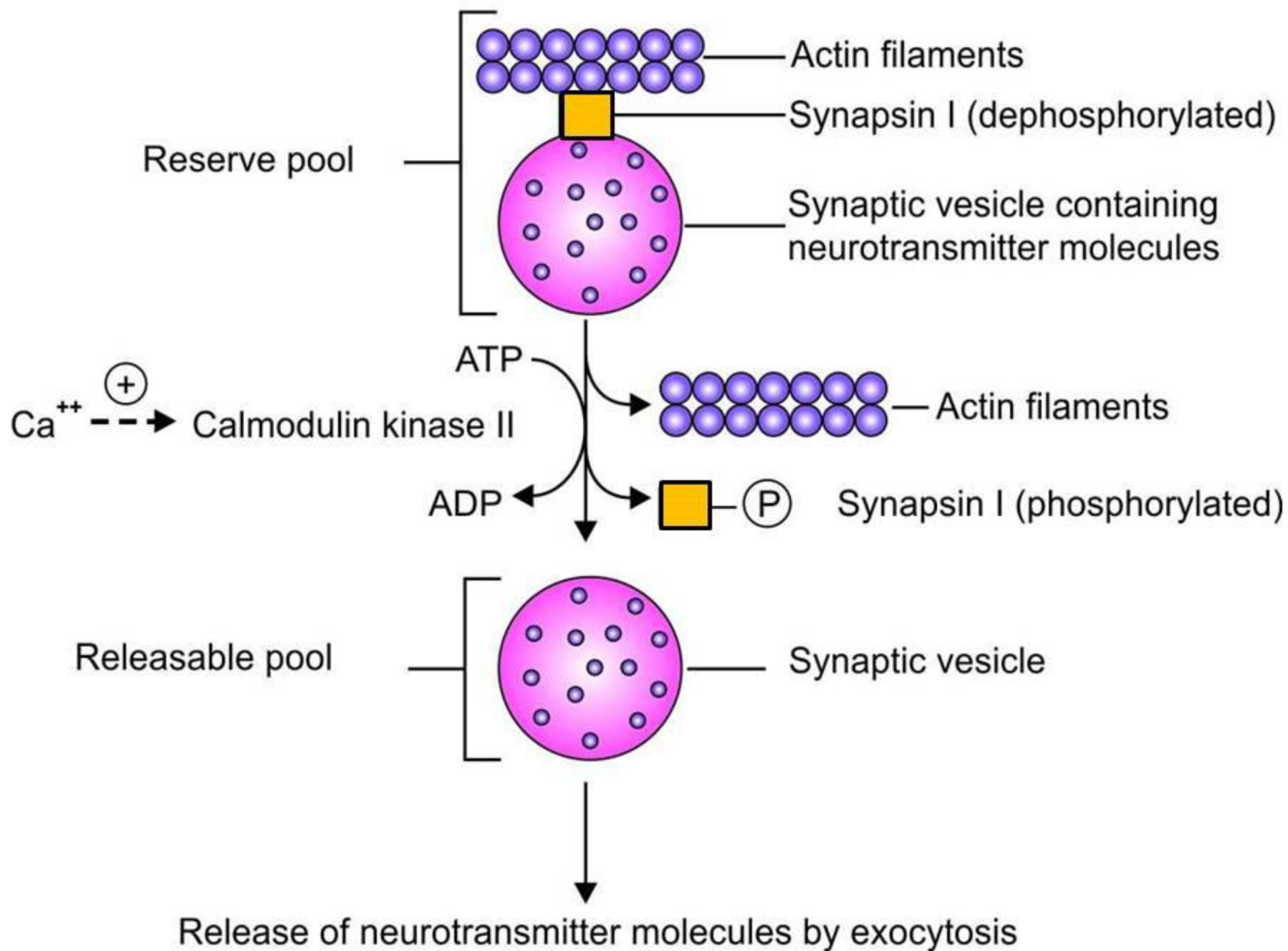
There are two pools of synaptic vesicles, reserve pool and releasable pool

In the reserve pool, a synaptic vesicle is bound to actin filaments through a protein, synapsin I (dephosphorylated)

Release of Ca^{++} activates calmodulin (CaM) kinase II which phosphorylates synapsin I

This leads to dissociation of the synaptic vesicle from actin filaments

Synaptic vesicle moves to releasable pool from where it releases the neurotransmitter molecules by exocytosis



Neuromuscular transmission

Neuromuscular transmission occurs through release of acetylcholine from the motor endplate

This occurs in the presence of calcium ions

Excitability and contractility of myocardium

- The rhythmic generation of impulses in heart and contraction of heart muscle also require calcium ions
- An increase in the concentration of ionized calcium increases cardiac contractility and vice versa

Coagulation of blood

Ionized calcium is one of the coagulation factors

Coagulation of blood occurs by a cascade of reactions

Calcium ions are required in most of these reactions

Many of the anticoagulants used to prevent in vitro

Action of hormones

Ionized calcium acts as a second messenger for some of the hormones

Moreover, the secretion of hormones which are stored in granular form also requires the presence of calcium ions

Absorption

Absorption of calcium occurs by an active uptake system in the upper part of small intestine

Normally, 10-20% of the dietary calcium is absorbed

The absorption is affected by:

pH

Calcium : phosphorus ratio

Proteins

Vitamin D and parathormone

pH

A relatively low pH increases solubility of calcium salts

This increases calcium absorption

Calcium : phosphorus ratio

Since calcium and phosphorus are absorbed together, they must be present in the diet in a proper ratio

The ideal ratio is 1:1 but absorption can occur satisfactorily as long as the ratio lies between 1:2 and 2:1

Proteins

Presence of proteins and amino acids in the food together with calcium facilitates the absorption of calcium

Vitamin D and parathormone

Vitamin D and parathormone play an important role in the metabolism of calcium

Cholecalciferol is converted into its active metabolite, 1,25-dihydroxycholecalciferol with the help of parathormone

1,25-Dihydroxycholecalciferol acts on intestinal mucosa and induces the synthesis of:

- Calcium-binding protein
- Calcium- dependent ATPase
- Alkaline phosphatase

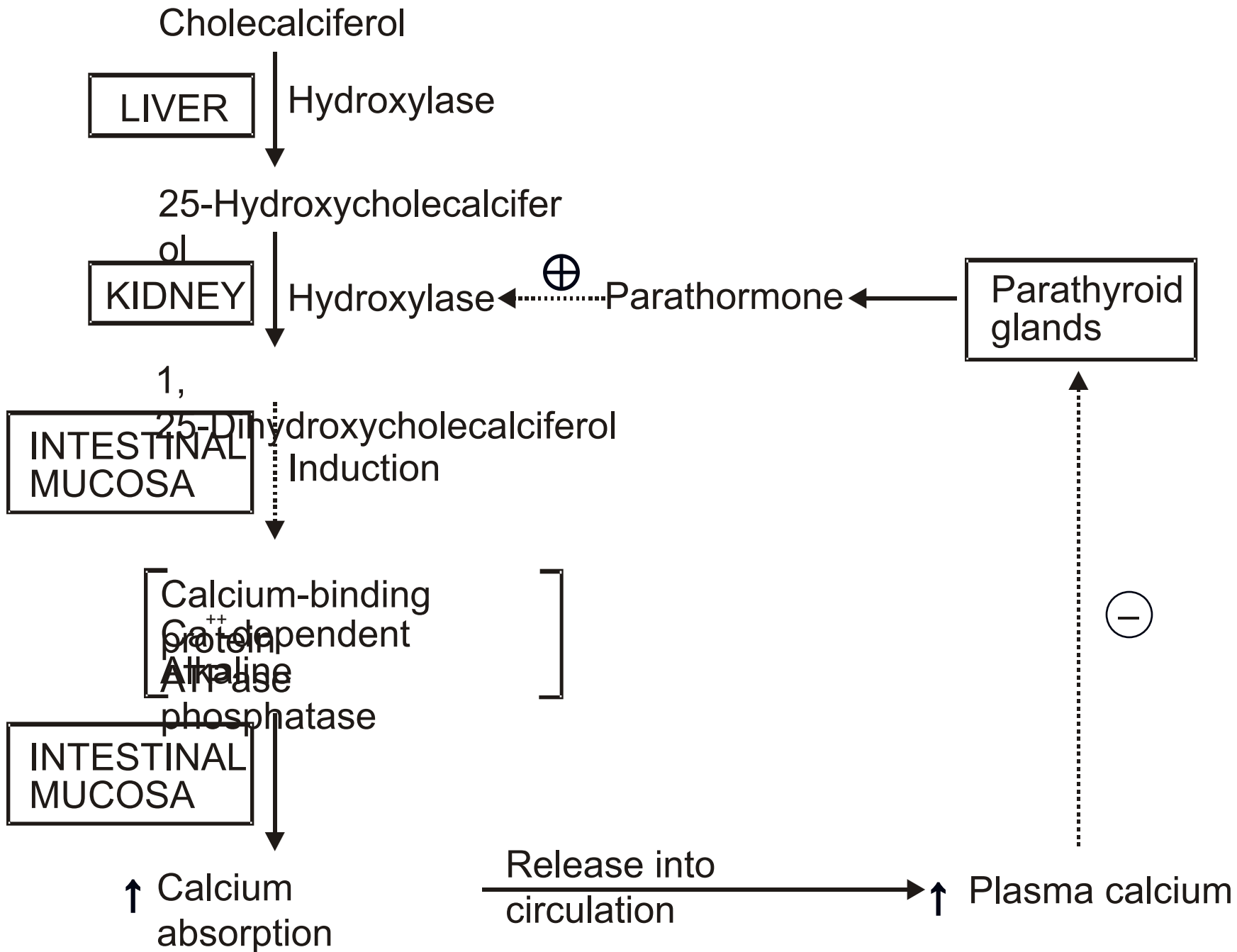
These are required for the active absorption of calcium

As calcium is absorbed, plasma calcium level rises

When plasma calcium rises above normal, it causes feedback inhibition of parathormone secretion

This switches off the series of reactions responsible for raising the plasma calcium level

Thus, vitamin D and parathormone act in concert to regulate calcium absorption and the plasma calcium level



Daily requirement

Age	Requirement
Infants	400-600 mg/day
Children	800 mg/day
Adolescents	1200 mg/day
Adults	800 mg/day
Pregnant and lactating women	1200 mg/day

Sources

Milk

Cheese

Eggs

Figs

Nuts

Beans

Lentils

Cabbage

Cauliflower

Abnormal serum calcium levels

Serum calcium level may rise or fall in some pathological conditions

An increase in serum calcium level is known as hypercalcaemia

A decrease in serum calcium level is known as hypocalcaemia

□ Hypercalcaemia occurs in:

- Hyperparathyroidism
- Hypervitaminosis D
- Bone cancer
- Multiple myeloma
- Leukaemia
- Polycythaemia
- Milk-alkali syndrome
- Sarcoidosis

Hypocalcaemia occurs in:

- Hypoparathyroidism
- Rickets
- Osteomalacia
- Steatorrhoea
- Chronic renal failure
- Nephrotic syndrome

1 If serum calcium level remains elevated over a long period, calcium may get deposited in soft tissues such as kidneys, liver, arteries etc

2 A sudden decrease in serum calcium may cause tetany (involuntary contraction of skeletal muscles)

Phosphorus

Next to calcium, phosphorus is the most abundant mineral in human beings

About 700 gm of phosphorus is present in an average adult

Nearly 80% of it is present in bones and teeth

The remainder is distributed all over the body

Nerves and muscles are particularly rich in phosphorus

Phosphorus is mainly an intracellular mineral

Serum inorganic phosphorus level is 2.5 - 4.0 mg/dl in adults and 4 - 7 mg/dl in children

The product of serum calcium concentration (mg/dl) and serum inorganic phosphorus concentration (mg/dl) remains nearly constant

Adults

Serum calcium X serum inorganic phosphorus =40

Children

Serum calcium X serum inorganic phosphorus =50

• **Functions**

- Formation of bones and teeth
- Formation of high-energy compounds
- Role in metabolism
- Formation of nucleic acids
- Formation of membranes
- Formation of nervous tissue
- Maintenance of pH

Formation of bones and teeth

- As seen earlier, calcium phosphate is the principal salt in bones and teeth
- Formation of bones and teeth is one of the major functions of phosphorus

Formation of high-energy compounds

Phosphorus is a constituent of most of the high-energy compounds in our body e.g. ATP, creatine phosphate, phosphoenol pyruvate etc

Role in metabolism

Phosphorus is a constituent of many coenzymes
e.g. FMN, FAD, NAD, NADP, thiamin pyrophosphate, pyridoxal phosphate and coenzyme A

Phosphorus plays an important role in metabolic reactions in the form of these coenzymes

Moreover, phosphorus plays a unique role in the metabolism of carbohydrates

Carbohydrates have to be phosphorylated before they can enter any metabolic pathway

Formation of nucleic acids

Phosphorus is required for the formation of nucleotides which, in turn, form nucleic acids

Formation of membranes

Phosphorus participates in the formation of bio-membranes in the form of phospholipids

Formation of nervous tissue

Phosphorus also takes part in the formation of nervous tissue in the form of phospholipids

Maintenance of pH

Inorganic phosphorus exists as HPO_4^{-2} and $\text{H}_2\text{PO}_4^{-}$ which constitute a buffer pair and help in the maintenance of pH

Phosphate buffer is more abundant in intracellular fluid

Absorption

Phosphorus is absorbed from the small intestine along with calcium

If calcium absorption is normal, so will be that of phosphorus

Daily requirement

Age	Requirement
Infants	250-400 mg/day
Children	800 mg/day
Adolescents	1200 mg/day
Adults	800 mg/day
Pregnant and lactating women	1200 mg/day

Dietary sources

Phosphorus is widely distributed in foodstuffs

If calorie and protein intakes are sufficient, a dietary deficiency of phosphorus is unlikely to occur

Milk, cheese, eggs, meat, nuts and beans are particularly good sources of phosphorus

Abnormal serum phosphorus levels

■ An increase in serum inorganic phosphorus level is known as hyperphosphataemia

■ A decrease in serum inorganic phosphorus level is known as hypophosphataemia

□ Hyperphosphataemia occurs in:

- Chronic renal failure
- Hypoparathyroidism
- Hypervitaminosis D
- Acromegaly
- Diabetes mellitus

□ Hypophosphataemia occurs in:

- Rickets
- Osteomalacia
- Hyperparathyroidism
- Steatorrhoea
- Fanconi syndrome and
- Familial hypophosphataemic rickets

1 Familial hypophosphataemic rickets is also known as renal rickets or vitamin D-resistant rickets

2 Renal rickets is an inherited disorder (X-linked dominant) in which renal tubular reabsorption of phosphate is greatly decreased

Magnesium

The total magnesium in an average adult is about 20 gm

Bones contain about 70% of the total body magnesium

The remainder is present in other tissues and body fluids e.g. muscles, blood, CSF etc

Serum magnesium level is 2 - 3 mg/dl

Concentration in intracellular compartment is higher than that in extracellular compartment

Functions

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graph TD; Functions[Functions] --- Excitability[Excitability of nerves]; Functions --- Cofactor[Cofactor for enzymes];
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Excitability of
nerves

Cofactor for
enzymes

Excitability of nerves

Together with some other cations, magnesium ions also affect the excitability of nerves

A low magnesium level increases the excitability, and a high magnesium level decreases the excitability

Cofactor for enzymes

Magnesium is a cofactor for all the enzymes requiring ATP

ATP participates in biochemical reactions as Mg^{++} -ATP complex

These include enzymes involved in the metabolism of:

- Carbohydrates
- Lipids
- Amino acids
- Purines
- Pyrimidines

Examples are:

- Hexokinase
- Phosphofructokinase
- Pyruvate kinase
- Thiokinase
- Mevalonate kinase
- Squalene synthetase
- Glutamine synthetase
- Carbamoyl phosphate synthetase
- PRPP synthetase

Absorption

1 Magnesium is absorbed from the small intestine

2 The extent of absorption depends on the magnesium content of the diet and is independent of the requirement

3 On an average diet, about half of the ingested magnesium is absorbed

The absorption may increase on a low-magnesium diet, and may fall on a high-magnesium diet

The regulation of magnesium balance is the function of kidneys

Aldosterone plays a role in the renal regulation

A high aldosterone level decreases the tubular

Daily requirement

Age and sex	Requirement
Infants	60-70 mg/day
Children	150-250 mg/day
Adult men	350 mg/day
Adult women	300 mg/day
Pregnant and lactating women	450 mg/day

Dietary sources

Nuts, beans, wheat, milk, eggs, orange and spinach are good sources of magnesium

Almond is particularly rich in magnesium

Abnormal serum magnesium levels

1 Serum magnesium level is decreased (hypomagnesaemia) in chronic alcoholism, chronic diarrhoea, hyperparathyroidism and aldosteronism

2 A high serum magnesium level (hypermagnesaemia) is commonly seen in renal failure

Sodium

Total amount of sodium in an average adult is about 60 gm

About 20 gm is present in bones

The rest is distributed in other tissues

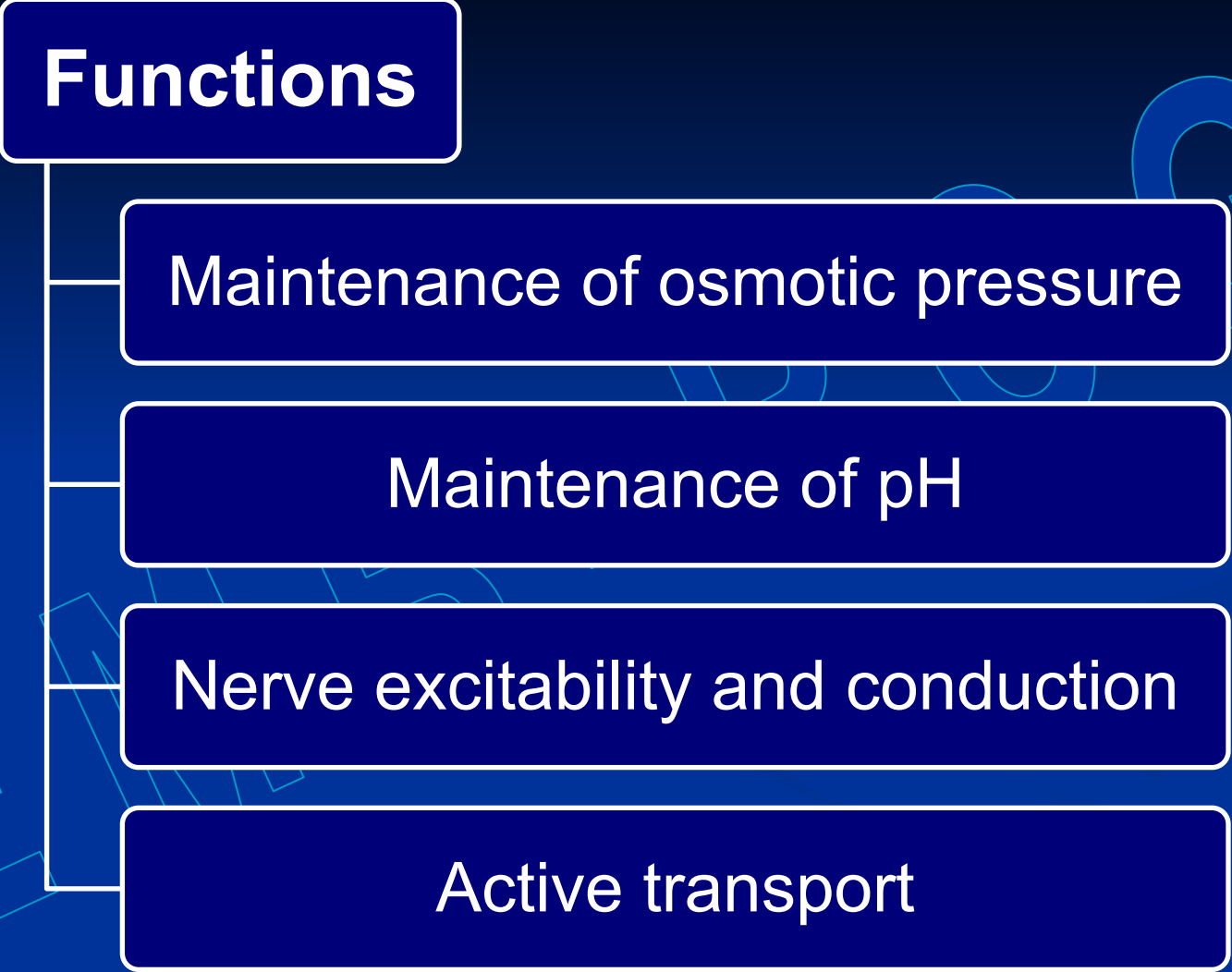
Sodium is the major cation of the extracellular fluids

Plasma sodium level is 310-340 mg/dl or 136-145 mEq/L

Other extracellular fluids also have a high concentration

The intracellular fluid contains only about 10 mEq/L

Functions



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graph TD; A[Functions] --- B[Maintenance of osmotic pressure]; A --- C[Maintenance of pH]; A --- D[Nerve excitability and conduction]; A --- E[Active transport];
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Maintenance of osmotic pressure

Maintenance of pH

Nerve excitability and conduction

Active transport

Maintenance of osmotic pressure

- Being the major cation of extracellular fluids, sodium plays an important role in maintaining the osmotic pressure of extracellular fluids
- Osmotic pressure depends upon the number of solute particles and not on their size
- Sodium ions outnumber all the other solute particles in extracellular fluids

Maintenance of pH

In the form of sodium bicarbonate, it is a component of the bicarbonate-carbonic acid buffer which is a major buffer of the extracellular fluids

Renal excretion of hydrogen ions in exchange for sodium ions is also important in maintaining the pH of body fluids

Nerve excitability and conduction

- Maintenance of normal excitability of nerves and conduction of nerve impulses are also important functions of sodium
- Cations and anions are so distributed across the cell membrane of nerve fibres that the exterior of the membrane is slightly electropositive in relation to the interior

1 This potential difference is known as the resting potential

2 When a stimulus is applied to the nerve, the stimulated area immediately becomes permeable to sodium ions which move into the interior of the nerve fibre

3 The interior becomes electropositive in relation to the exterior

Thus, a nerve impulse is generated

Transmission of the nerve impulse also occurs due to influx of sodium ions along the entire length of the nerve fibre

Active transport

- Several compounds enter the cells against their concentration gradient by active absorption
- Sodium pump ejects sodium ions from the interior of the cell to the exterior
- It is linked with the active absorption of glucose, galactose and some amino acids

Absorption

Sodium enters gastrointestinal tract through ingested food and through digestive secretions

The latter is a far more abundant source as compared to dietary intake

Almost all the sodium is absorbed from the gastro-intestinal tract

The absorption occurs from the entire length of the small and large intestines

Concentration of sodium in intestinal lumen is far greater than that inside the mucosal cells

Sodium diffuses from the lumen into the cells down its concentration gradient

The intracellular sodium is actively transported into blood by the sodium pump

1 Pumping of Na^+ into blood keeps intracellular concentration of sodium in the mucosal cells at a low level

2 More sodium diffuses from the intestinal lumen into the mucosal cells

Requirement

- There has been considerable controversy about the daily requirement of sodium
- The requirement depends upon daily loss of sodium
- The loss depends upon the climate

In a tropical country like India, a daily intake of 4-6 gm of elemental sodium or 10-15 gm of sodium chloride is sufficient to maintain sodium balance

A direct relationship exists between excessive sodium intake and prevalence of hypertension

We have to guard against excessive intake rather than deficiency

Dietary sources

Table salt (sodium chloride) is one of the chief sources of sodium in our daily diet

Baking powder (sodium bicarbonate) can also contribute significant amounts

Meat, fish, fowl, eggs, milk, cheese and cereals are rich in sodium

Carrot, radish, cauliflower, spinach, turnip, legumes and nuts are also good sources of sodium

Abnormal serum sodium levels

- 1 Sodium metabolism is controlled by adrenocortical hormones
- 2 Mineralocorticoids, such as aldosterone, are the most potent in this regard followed by glucocorticoids and sex hormones

These hormones cause retention of sodium and loss of potassium from the body

Therefore, abnormal serum sodium levels occur in adrenocortical disorders

Excessive loss of sodium in gastrointestinal secretions and urine can also affect the serum sodium level

Hyponatraemia (low serum sodium) occurs in adrenocortical insufficiency, severe diarrhoea, chronic renal disease, excessive sweating etc

Hyponatraemia may also occur due to dilution of plasma when dehydrated patients are rehydrated with salt-free fluids

Hypernatraemia (high serum sodium) occurs in adrenocortical hyperactivity, prolonged steroid therapy and dehydration

In dehydration, hypernatraemia occurs due to haemoconcentration

Potassium

Total amount of potassium in an average adult is about 140 gm

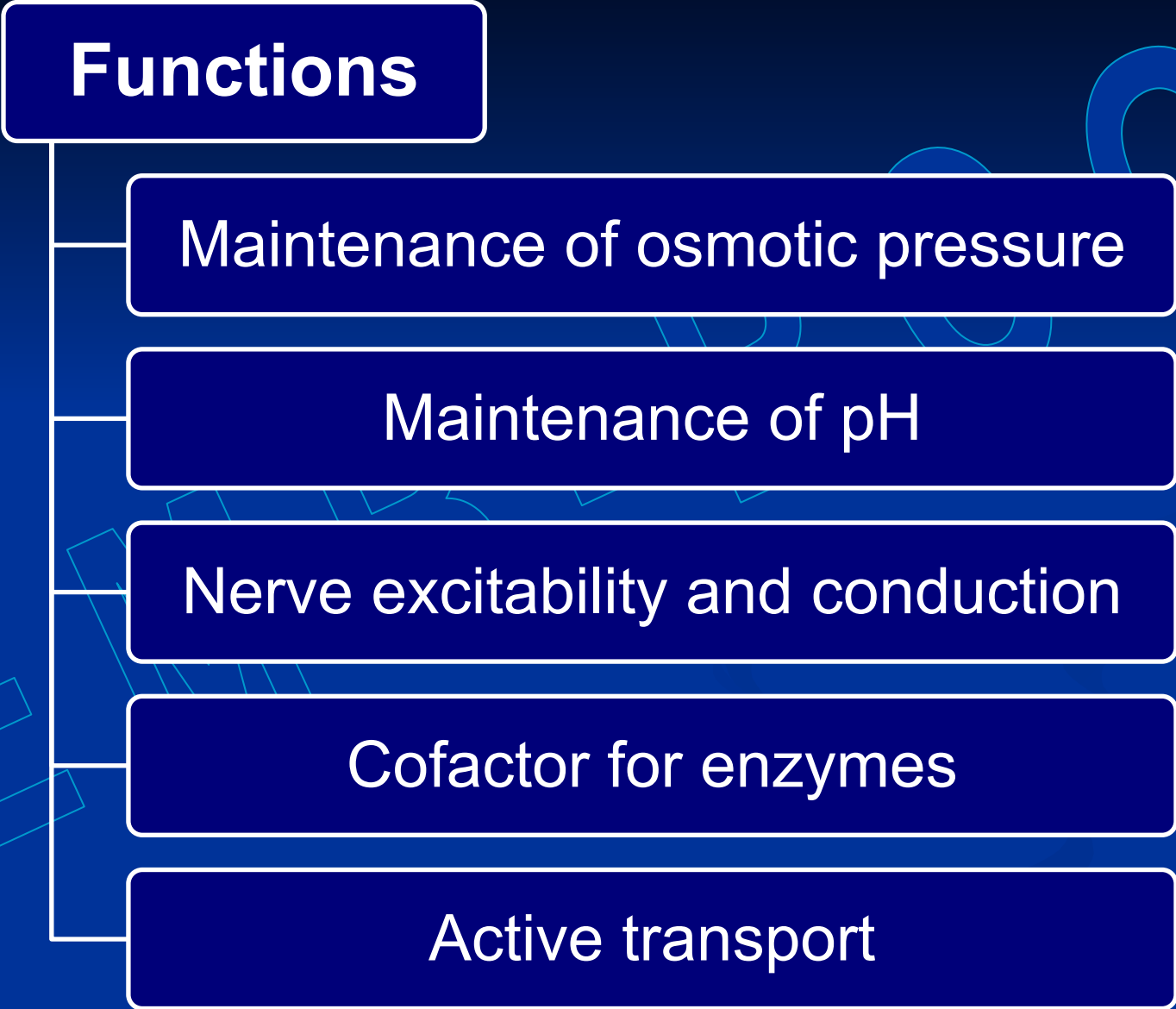
Potassium is the chief cation of the intracellular compartment, and is present in all cells

The potassium content of intracellular fluid is about 140 mEq/L

Potassium concentration in extracellular fluid is only about 5 mEq/L

Serum potassium level is 3.5-5 mEq/L

Functions



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graph TD; A[Functions] --- B[Maintenance of osmotic pressure]; A --- C[Maintenance of pH]; A --- D[Nerve excitability and conduction]; A --- E[Cofactor for enzymes]; A --- F[Active transport];
```

Maintenance of osmotic pressure

Maintenance of pH

Nerve excitability and conduction

Cofactor for enzymes

Active transport

Maintenance of osmotic pressure

1 Potassium is involved in the maintenance of osmotic pressure within the cells in the same way as sodium does in extracellular compartment

2 Nearly half the osmolarity of intracellular fluid is due to potassium

Maintenance of pH

Potassium, in the form of KH_2PO_4 and K_2HPO_4 , helps to maintain the pH of intracellular fluid

Nerve excitability and conduction

Together with sodium, potassium plays a role in maintaining the normal excitability of nerves and in the conduction of nerve impulses

It also affects the excitability and contractility of muscles, particularly heart muscles

Marked alterations in serum potassium level often cause serious abnormalities in the functioning of the

Cofactor for enzymes

1 Potassium functions as a cofactor for some enzymes e.g. pyruvate kinase

Active transport

- Along with sodium, potassium is also involved in active transport
- Sodium pump is involved in energy-dependent active transport of glucose, galactose, amino acids etc
- It is really a sodium-potassium pump as it causes efflux of sodium and influx of potassium

Absorption

Potassium absorption occurs down the concentration gradient from small intestine as well as large intestine

Requirement

- The exact potassium requirement is not known with certainty
- A daily intake of 4 gm is sufficient to maintain potassium balance

Dietary sources

Potassium is very widely distributed in foodstuffs

Meat, fish, fowl, cereals, vegetables, apricots, peaches, oranges and pineapples are rich in potassium

Abnormal serum potassium levels

A decrease in serum potassium level is known as hypokalaemia

An increase in serum potassium level is known as hyperkalaemia

Both affect nervous system, heart and muscles, and produce characteristic ECG changes

□ Hypokalaemia occurs in :

- Adrenocortical hyperactivity
- Prolonged steroid therapy
- Diarrhoea
- Wasting diseases
- Metabolic alkalosis
- Familial periodic paralysis
- After insulin injection
- Prolonged use of thiazide diuretics

Hypokalaemia can cause:

- Irritability
- Muscular weakness
- Tachycardia
- Cardiac dilatation
- Cardiac arrest

Hypokalaemia also produces characteristic electrocardiographic changes :

- Flattened or inverted T waves
- Depressed ST segment

These changes are valuable in the diagnosis of potassium deficit

Hyperkalaemia occurs in:

- Adrenocortical insufficiency
- Renal failure
- Dehydration
- Indiscriminate intravenous potassium therapy

Hyperkalaemia causes:

- Mental confusion
- Numbness and tingling
- Muscular weakness and paralysis
- Bradycardia
- Peripheral circulatory failure
- Cardiac arrest

Characteristic electrocardiographic changes are:

- Lengthening of P-R interval
- Widening of QRS complex
- Elevation of T waves

Chlorine

The total amount of chlorine in an average adult is about 80 gm

Chlorine, in the form of chloride ions, is the chief anion of extracellular compartment

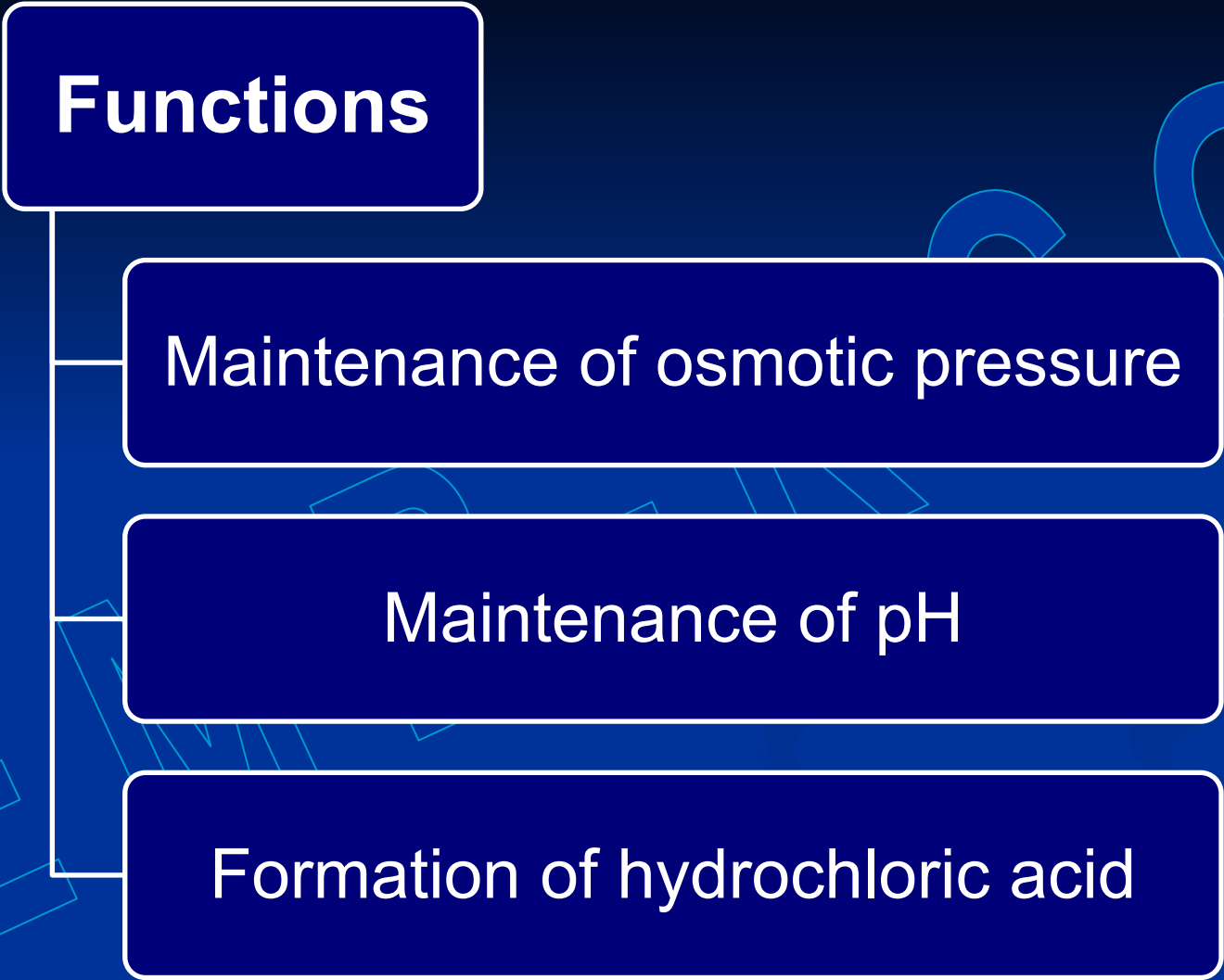
Normal serum chloride level is 100-106 mEq/L (355-375 mg/dl)

The chloride content of cerebrospinal fluid is 120 to 130 mEq/L

The interstitial fluid contains about 110 mEq/L

The intracellular fluid contains only about 4 mEq/L

Functions



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graph TD; A[Functions] --- B[Maintenance of osmotic pressure]; A --- C[Maintenance of pH]; A --- D[Formation of hydrochloric acid]
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Maintenance of osmotic pressure

Maintenance of pH

Formation of hydrochloric acid

Maintenance of osmotic pressure

Chloride ions are present in a high concentration in extracellular fluids

Along with sodium ions, they play an important role in maintaining the osmotic pressure of extracellular fluids

Maintenance of pH

Chloride ions help in maintaining the pH of blood by the mechanism of chloride shift

Formation of hydrochloric acid

Hydrochloric acid is an important constituent of gastric juice

Chloride ions are required for its formation

Absorption

Chloride is absorbed passively down its concentration gradient in the upper portion of small intestine

In distal ileum and colon, chloride ions are absorbed in exchange for bicarbonate ions

Requirement

- Chloride is commonly present in food as sodium chloride
- Therefore, sodium and chloride intakes are parallel
- If daily requirement of sodium is met, so will be that of chloride

Dietary sources

Table salt is the most abundant source of chloride in our daily diet

Foods having sodium also provide chloride e.g. meat, fish, fowl, eggs, milk, cheese, cereals etc

Abnormal serum chloride levels

With a few exceptions, changes in serum chloride level are parallel to those in serum sodium level

Serum chloride level is raised (hyperchloraemia) in dehydration, respiratory alkalosis, metabolic acidosis and adrenocortical hyperactivity

1 Serum chloride level is decreased
(hypochloraemia) in severe vomiting, prolonged
gastric suction, respiratory acidosis, metabolic
alkalosis and Addison's disease

Sulphur

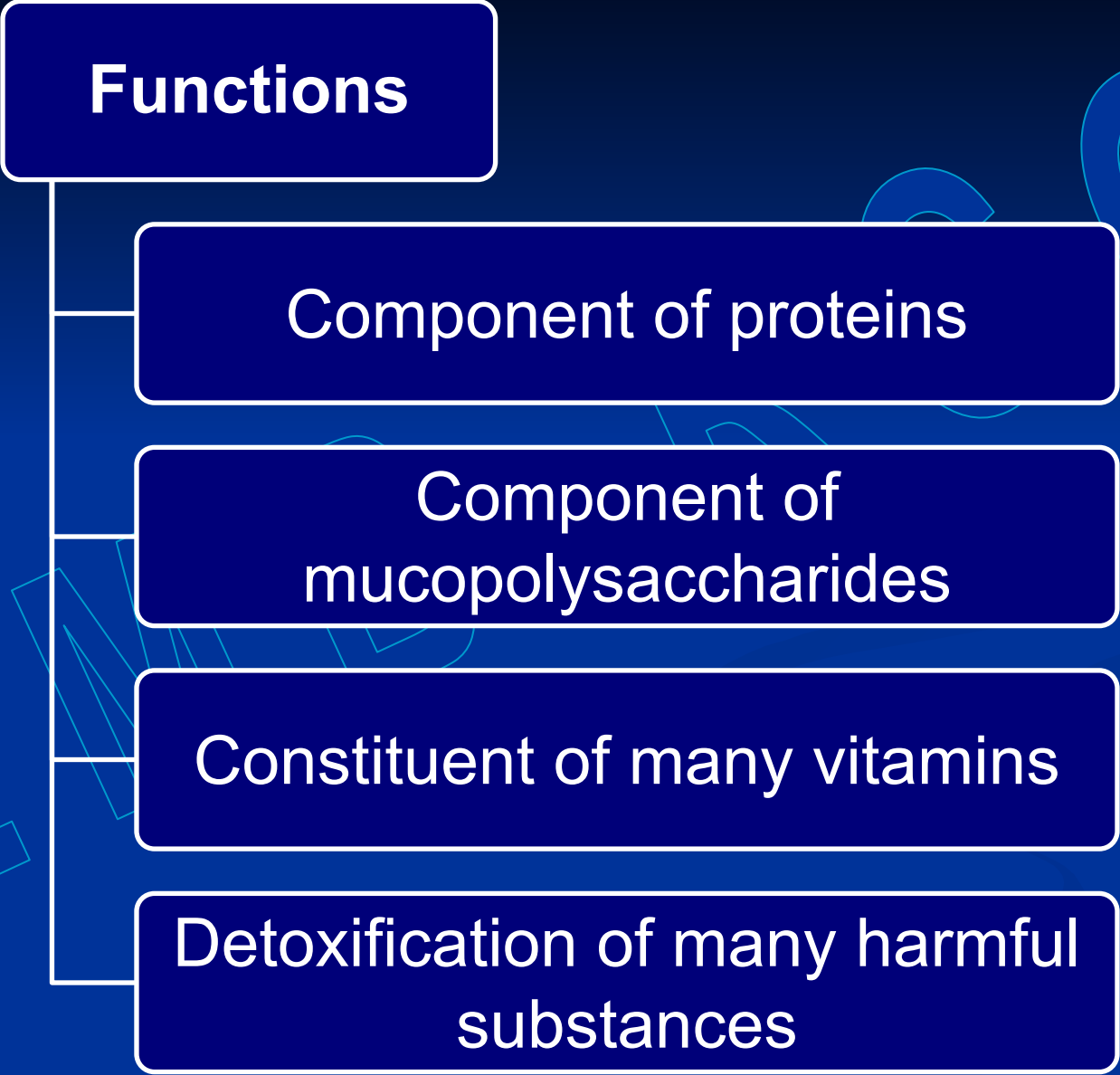
About 100 gm of sulphur is present in an average adult

Inorganic sulphur, in the form of sulphate ions, is present in very small amounts

Organic sulphur is the predominant form of sulphur in the body

It is present in most proteins in the form of sulphur-containing amino acids

Functions



Component of proteins

Component of
mucopolysaccharides

Constituent of many vitamins

Detoxification of many harmful
substances

Sulphur is a component of most of the proteins in the form of cysteine and methionine

The sulphhydryl ($-SH$) groups of cysteine residues stabilize the structure of proteins by forming disulphide bonds

They are also essential for the biological activity of many proteins, particularly enzymes

- Several mucopolysaccharides, e.g. heparin, chondroitin sulphate and keratan sulphate, contain sulphur
- Sulphur is a constituent of many vitamins e.g. thiamin, biotin, lipoic acid etc
- Active form of pantothenic acid, i.e. coenzyme A and acyl carrier protein, also contain sulphur

Detoxification of many harmful substances is done in liver by conjugation reactions

Several such substances are conjugated with sulphate

Absorption

Sulphur is absorbed from the intestine mainly in the form of sulphur-containing amino acids

Absorption of inorganic sulphate is very poor

Requirement

The daily excretion of sulphur is about 5 gm in average adults

Most of it is derived from proteins

If protein intake is adequate, it will provide sufficient sulphur as well

Dietary sources

It is the sulphur of the proteins that meets our sulphur requirements

Therefore, protein-rich foods, e.g. eggs, milk, cheese, meat, fish, nuts and legumes, are the main sources of sulphur in our daily diet

Iron

Total amount of iron in an adult human being is 3.5-4.5 gm

Blood and blood-forming organs are the largest reservoirs of iron in our body

But small amounts of iron are present in nearly every tissue

□ Important iron-containing compounds are:

- Haemoglobin
- Myoglobin
- Ferritin
- Haemosiderin
- Transferrin
- Cytochromes
- Iron-containing enzymes

About 70% of the body iron is present in haemoglobin and 5% in myoglobin

Ferritin and haemosiderin, which are storage forms of iron, contain about 20% of the body iron

Transferrin, an iron carrier protein present in plasma, contains 0.1% of the body iron

The remaining iron is present in cytochromes and enzymes

Haemoglobin

Haemoglobin is a tetramer made up of four subunits

Each subunit contains one iron atom

Myoglobin

Myoglobin is present in muscles

It is a monomer having one iron atom

Cytochromes

Cytochromes are present in respiratory chain, and support tissue respiration

Cytochrome P-450 and cytochrome b_5 are components of microsomal hydroxylase system

Ferritin

Ferritin is present in liver, spleen, bone marrow, brain, kidneys, intestine, placenta etc

It is one of the storage forms of iron

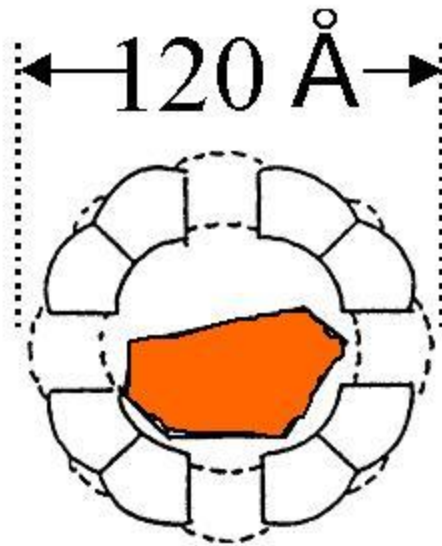
The protein portion is known as apoferritin

Apoferritin combines with iron to form ferritin

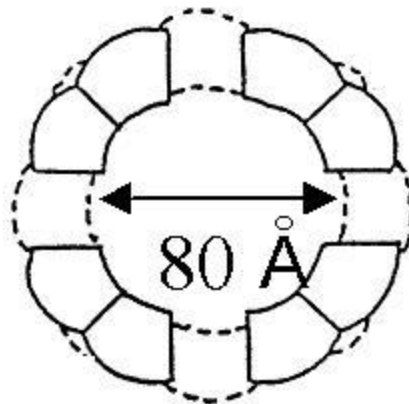
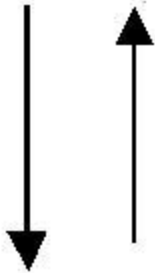
The first step in the synthesis of ferritin is the formation of apoferritin induced by the entry of ferrous iron in the cell

This is followed by oxidation of ferrous iron to the ferric form

Ferric iron forms ferric hydrophosphate micelles, which enter the protein shell to form ferritin



Ferritin



Apo-ferritin

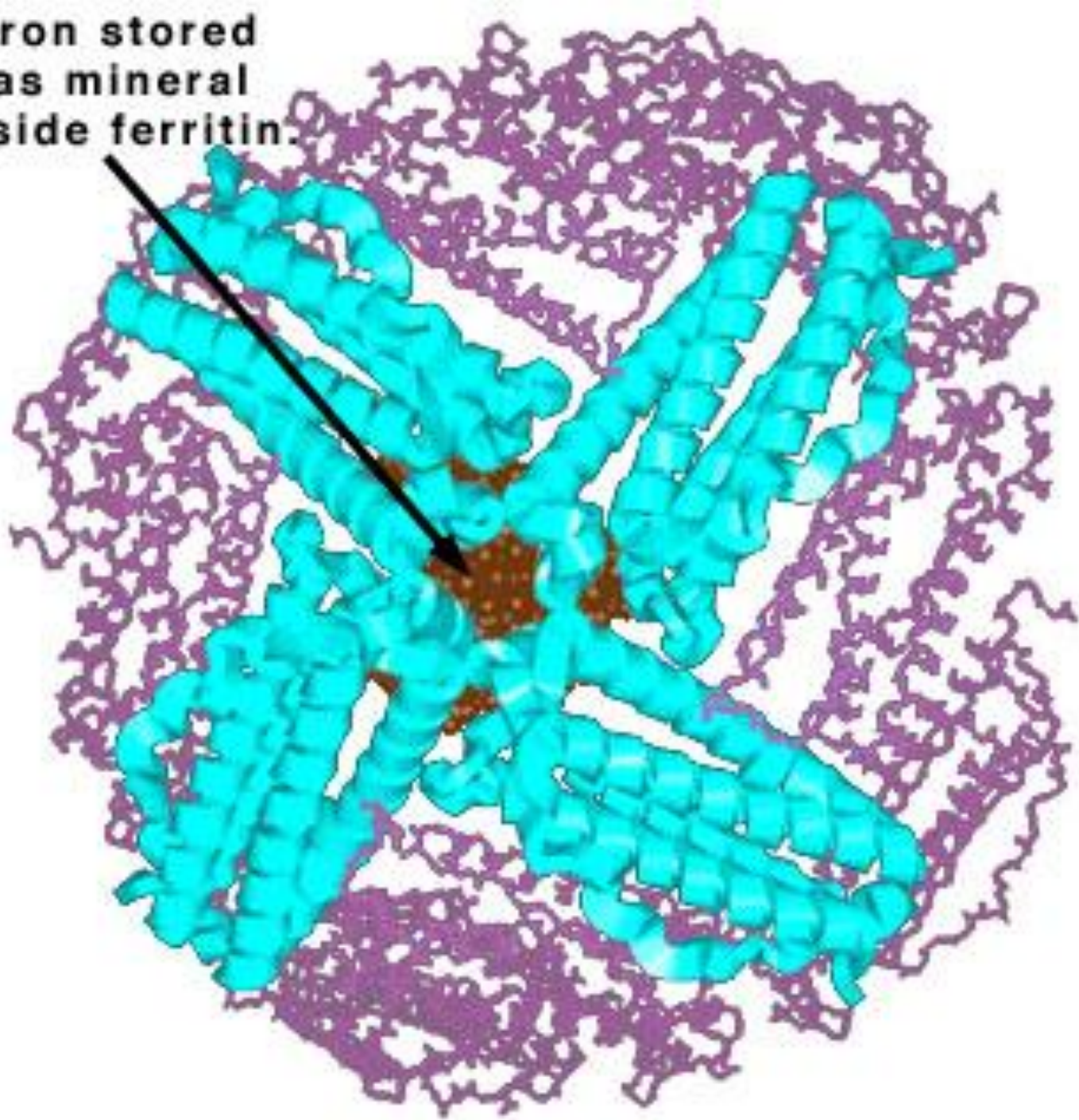
Apoferritin is made up of 24 identical subunits, each having a molecular weight of 22,000 to 24,000

The subunits are arranged at the vertices of a pentagonal dodecahedron with a hollow space in the centre

Ferric hydrophosphate micelles are present in this space

When fully saturated, a molecule of ferritin contains 5,000 atoms of iron, and has a molecular weight of 900,000

Iron stored
as mineral
inside ferritin.



Haemosiderin

Haemosiderin is a granular iron-rich protein

It is insoluble in water unlike ferritin

The exact structure of haemosiderin is not known

It has been shown that iron is first stored in the body in the form of ferritin

As the iron stores increase, the older ferritin molecules are aggregated to form haemosiderin

Some of the protein is degraded in this process

Therefore, the percentage of iron in haemosiderin is higher as compared to that in ferritin

Normally, about two thirds of the stored iron is in the form of ferritin and one third in the form of

Transferrin

- Transferrin is a carrier protein which transports iron in circulation
- Free iron is toxic, and has a tendency to precipitate
- These problems are overcome by combining iron with transferrin

Transferrin is a β_1 -globulin with a molecular weight of about 90,000

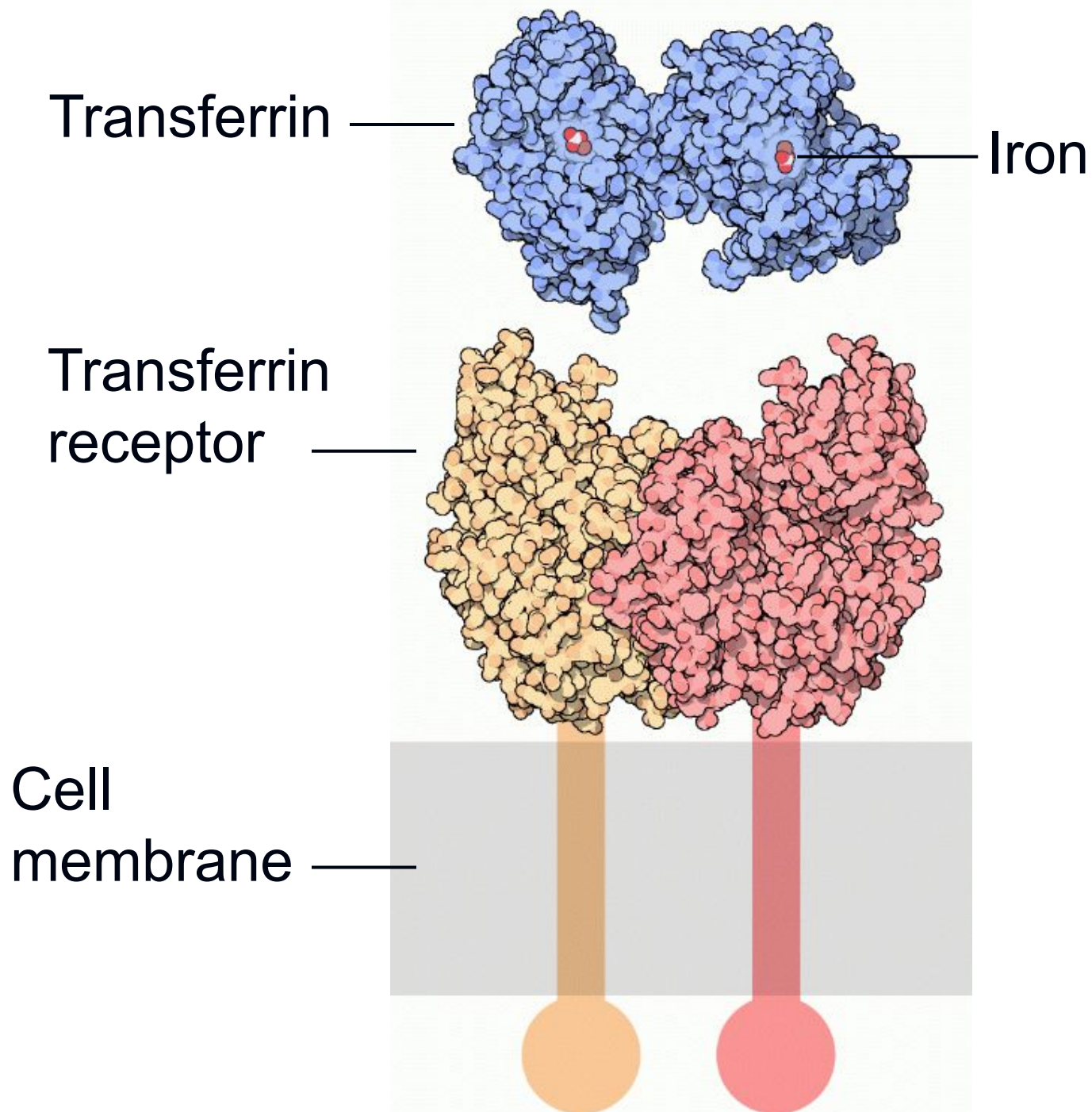
It is made up of two non-identical subunits

One molecule of transferrin can transport two ferric atoms

Transferrin carries iron to and from various tissues through circulation

There are specific receptors for transferrin on the cell membranes of the cells requiring iron e.g. red cell precursors

Transferrin-iron complex binds to these receptors



1 The binding produces a conformational change in the transferrin molecule as a result of which the iron is released

2 The free transferrin molecule is then displaced from the receptor by molecules carrying iron

The concentration of transferrin in plasma is 200-400 mg/dl

This amount of transferrin is capable of carrying 250-400 mg of iron per dl of plasma

This is known as the total iron binding capacity of plasma

Normal plasma iron level is 50-175 $\mu\text{g/dl}$

This means that the iron binding capacity of plasma is only about 30% saturated in healthy subjects

Iron-containing enzymes

- Several enzymes require iron for their catalytic activity
- In some cases, iron forms an integral part of the enzyme molecules
- In others, presence of iron is required for the catalytic activity of the enzymes

The iron-containing enzymes are mostly concerned with biological oxidation

Examples of such enzymes are catalase, peroxidase, aconitase, succinate dehydrogenase, xanthine oxidase etc

Functions

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graph TD; A[Functions] --- B[Transport of oxygen]; A --- C[Oxidative reactions]; A --- D[Tissue respiration]
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Transport of oxygen

Oxidative reactions

Tissue respiration

Transport of oxygen

The most important function of iron is to transport oxygen in the body in the form of haemoglobin

A similar function is performed in muscles by myoglobin

Oxidative reactions

Iron is a component of various oxidoreductase enzymes

As such, it plays a role in a number of oxidative reactions

Tissue respiration

- As a component of cytochromes in the respiratory chain, iron is involved in tissue respiration
- It is the iron component of the cytochromes that accepts and donates electrons

Iron balance

Iron status depends upon the relative rates of iron absorption and iron excretion

Iron absorption is the major mechanism for maintaining normal iron balance

Iron metabolism is said to occur within a closed system in the body

There is hardly any exchange of iron between man and his environment

The iron present in the body is continuously reutilized

Only a minute amount of iron is lost everyday from the body in the form of exfoliated cells

The faecal iron loss is 0.4-0.5 mg a day

The urinary iron loss is about 0.1 mg a day

About 0.2-0.3 mg of iron is lost daily from the skin along with the exfoliated cells

Thus, the total iron loss is just under one mg a day

In premenopausal women, there are two additional routes of iron loss

About 20-25 mg of iron is lost with menstrual blood in each cycle

This is equivalent to a daily loss of 0.7-0.8 mg of iron

During pregnancy, there is no menstrual loss but the expectant mother provides iron to the foetus

The transfer of iron to the foetus is about:

0.6 mg a day in the first trimester

2.8 mg a day in the second trimester

4.0 mg a day in the third trimester

Iron loss is balanced by intestinal absorption

Intestinal absorption of iron is affected by:

- Body iron stores
- Erythropoietic activity
- Degree of saturation of plasma transferrin
- The amount of dietary iron
- Valency of ingested iron (Fe^{+2} or Fe^{+3})
- Presence of other substances in the food

Absorption is more when:

- Body iron stores are low
- Erythropoietic activity is high
- Saturation of plasma transferrin is low
- Iron is ingested in ferrous form

□ Iron absorption is increased by the presence of :

- Ascorbic acid
- Succinic acid
- Histidine
- Cysteine

□ Iron absorption is decreased by the presence of :

- Phytates
- Phosphates

Iron can be absorbed from all segments of the small intestine but presence and normal functioning of stomach are also essential

Patients with achlorhydria and those who have undergone gastrectomy absorb less iron as compared to normal persons

Gastric enzymes and hydrochloric acid release iron from iron-containing compounds and reduce ferric iron to the ferrous form

It is believed that ferritin content of mucosal cells of the intestine regulates the absorption of iron

These cells are formed in the crypts of Leiberkuhn

They gradually reach the tip of the villi and are shed off into the intestinal lumen

Their average life-span is three days

The function of ferritin in these cells is to block the absorption of iron

Those cells which are formed during a period of iron overload are rich in ferritin

These cells will absorb little iron during their life-span

Moreover, when these are shed off, their iron content will also be lost in faeces

Conversely, the cells formed during a period of iron deficiency are poor in ferritin

These cells absorb more iron and transfer it into the plasma

Requirement

Only a small proportion of the dietary iron is normally absorbed

Therefore, much larger amounts have to be provided in diet than the actual requirement

Age and sex	Requirement
Infants	6-10 mg/day
Children	10 mg/day
Adolescents	12 mg/day
Adult men and postmenopausal women	10 mg/day
Premenopausal and lactating women	15 mg/day
Pregnant women	30 mg/day

Dietary sources

1 Liver, heart, kidney, spleen, meat, fish and eggs are good sources of iron

2 The vegetable sources include whole wheat, figs, dates, nuts, beans, spinach, molasses etc

1 Much greater proportion of iron is absorbed from animal foods than from vegetable foods

2 On a mixed diet, healthy subjects absorb 5-10% of the dietary iron

Iron deficiency

- Iron deficiency is widespread both in poor and in affluent countries
- Iron deficiency is the commonest cause of anaemia throughout the world

Deficiency can be caused by :

Inadequate intake

Malabsorption

Blood loss

Inadequate intake is likely when requirement is high e.g. in:

Infancy

Adolescence

Pregnancy

Malabsorption can be due to:

Steatorrhoea

Coeliac disease

Gastrectomy

Persistent blood loss can occur from:

Genital tract

Gastrointestinal tract

Hookworm infestation

When iron deficiency develops, the earliest change is a depletion of body iron stores

Other changes follow progressively

Plasma transferrin saturation is decreased

Plasma iron is decreased

A microcytic, hypochromic anaemia develops

Poikilocytosis becomes evident

Hemoglobin level falls

Severe and prolonged deficiency leads to :

Koilonychia

Angular stomatitis

Glossitis

Pharyngeal and oesophageal webs

Atrophic gastritis

Partial villus atrophy

Iron overload

Iron overload is much less common than iron deficiency

Two types of iron overload syndromes are known:

- Haemosiderosis
- Haemochromatosis

Haemosiderosis

- Excess iron is deposited in reticulo-endothelial cells
- There is no tissue damage
- Excess iron enters the body through the parenteral route
- This can be due to repeated blood transfusions

Haemochromatosis

Excess iron enters the body through the alimentary route

It gets deposited in parenchymal cells and causes tissue damage

It may be primary or secondary

The gene responsible for primary haemochromatosis has not been identified

The genetic defect leads to excessive intestinal absorption of iron

Excess iron is deposited in liver, heart, pancreas and other endocrine glands, skin etc

The condition is also known as bronzed diabetes

Clinical abnormalities in bronzed diabetes are:

- Hepatomegaly
- Cardiomegaly
- Congestive heart failure
- Hypogonadism
- Diabetes mellitus
- Bronze-coloured pigmentation of skin

1 Serum iron, ferritin and per cent saturation of iron-binding capacity are increased in haemochromatosis

2 Phlebotomy and iron-chelating agents e.g. desferrioxamine are used to remove excess iron

Secondary haemochromatosis may occur in alcoholic liver disease in which iron deposition is usually confined to hepatic tissue

South African Bantus are known to develop haemochromatosis due to excessive ingestion of iron present in an alcoholic beverage brewed in iron vessels

Iodine

Total iodine in an average adult is 45-50 mg

About 10-15 mg is present in the thyroid gland

Muscles contain about 25 mg

About 5 mg is present in skin, 3 mg in the skeleton
and 2 mg in liver

Functions

- The only known function of iodine is in the synthesis of thyroid hormones
- The thyroid gland synthesizes tri-iodo-thyronine(T_3) and tetra-iodo-thyronine(T_4)
- These are synthesized from iodine and tyrosine residues of thyroglobulin

The thyroid gland:

- Actively takes up iodide ions from plasma
- Oxidises them to iodine
- Incorporates iodine into tyrosine residues of thyroglobulin
- The products are mono-iodo-tyrosine (MIT) and di-iodo-tyrosine (DIT)

Two DIT residues combine to form thyroxine (T_4)

One MIT and one DIT residues combine to form tri-iodo-thyronine (T_3)

Absorption

Iodine is absorbed from all parts of the alimentary tract, particularly from the small intestine

Iodine and iodate are converted into iodide prior to absorption

Other mucous membranes and skin can also absorb iodine

1 The iodide absorbed from the alimentary tract and elsewhere enters the circulation

2 About one third is taken up by the thyroid gland

3 The remainder is excreted, mainly by the kidneys

4 Small amounts of iodide are excreted in saliva, bile, milk, sweat and expired air

Plasma iodine level is 4-10 $\mu\text{g/dl}$

Only 10% of it is present in the form of inorganic iodide

Organic iodine is present mostly in the form of thyroid hormones

Thyroid hormones are bound to some proteins
(protein bound iodine)

Daily requirement

Age	Requirement
Infants	40-50 $\mu\text{g/day}$
Children	70-120 $\mu\text{g/day}$
Adults	150 $\mu\text{g/day}$

Dietary sources

Iodine is present in water and soil

Foods, both animal and plant, obtain iodine from water and soil

Iodine content of foodstuffs depends upon the iodine content of water and soil

Sea water is rich in iodine

Therefore, sea foods, e.g. fish, oysters, lobsters etc, are the best sources of iodine

As we go away from the sea, the iodine content of water and soil, and hence of the foodstuffs, decreases

Iodine deficiency

- Iodine deficiency is common in certain areas of the world
- These areas constitute the so-called goitre belt
- Sub-Himalayan region of India is a part of this belt as the iodine content of soil and water is poor in this region

A high prevalence of non-toxic goitre (endemic goitre) is seen in this region

Thyroid gland becomes hypertrophic in order to produce enough hormones from available iodine

A severe deficiency can produce hypothyroidism

Endemic goitre can be prevented by providing iodized table salt in the goitre belt

Iodized salt is prepared by mixing potassium iodate with common salt in the proportion of 1:10,000-20,000

Injection of iodized poppy seed oil has also been successfully used in some countries

One dose is sufficient for 2-4 years

Copper

- About 60-100 mg of copper is present in an average adult
- Relatively large amounts of copper are present in muscles (30-50 mg), bones (12-20 mg) and liver (9-15 mg)

Plasma copper level is 100-200 $\mu\text{g/dl}$

Nearly 90% of the plasma copper is tightly bound to ceruloplasmin

The rest is loosely attached to albumin

Albumin is the major carrier of copper as it can easily release copper

Many tissues contain minute amounts of copper in the form of copper-containing enzymes

Functions

Copper performs its physiological functions in the form of copper-containing enzymes

These include cytochrome oxidase, superoxide dismutase, monoamine oxidase, tyrosinase, dopamine hydroxylase etc

Ceruloplasmin also functions as ferroxidase which oxidises ferrous iron to the ferric form

□ Copper is also required for:

- Synthesis of haemoglobin
- Formation of bones
- Maintenance of myelin sheath of nerves

Absorption

■ About one third of the dietary copper is normally absorbed, mainly from small intestine

■ Copper-binding P-type ATPase, an enzyme present in intestinal mucosa (and many other cells) transfers copper into portal circulation

Albumin carries it to liver

A different copper-binding P-type ATPase present
in liver incorporates copper into apo-ceruloplasmin

Daily requirement

Adults require about 2.5 mg of copper daily

Infants and children require about 0.05 mg/kg of body weight

Sources

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graph TD; Sources --> Liver; Sources --> Kidney; Sources --> Meat; Sources --> Nuts; Sources --> Legumes; Sources --> Raisins;
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Liver

Kidney

Meat

Nuts

Legumes

Raisins

Disorders of copper metabolism

- Wilson's disease (hepatolenticular degeneration) is an autosomal recessive disease in which the synthesis of ceruloplasmin is impaired
- Large amounts of copper are deposited in liver, basal ganglia and around cornea
- Serum copper and ceruloplasmin levels are low

Urinary excretion of copper is increased

Recent work has shown that copper-binding P-type ATPase is congenitally deficient in liver in this disease

This impairs the incorporation of copper into apo-ceruloplasmin and its biliary excretion leading to copper toxicity

Another inherited disorder of copper metabolism is Menkes' disease which is an X-linked recessive disease

In this disease, copper-binding P-type ATPase is deficient in intestinal mucosa and most other tissues except liver

Copper accumulates in intestinal mucosa but can not be released into circulation

This leads to a deficiency of copper in tissues

The deficiency causes cerebral degeneration, hypochromic microcytic anaemia and steely or kinky hair

Serum copper and ceruloplasmin levels are elevated in:

- Pregnancy
- Infections
- Leukaemia
- Collagen diseases
- Myocardial infarction
- Cirrhosis of liver

Zinc

The total amount of zinc in an average adult is 1.3-2.1 gm

Its tissue distribution is very wide

Prostate, liver, kidneys, muscles, heart, skin, bones and teeth are particularly rich in zinc

Plasma zinc level is 50-150 $\mu\text{g/dl}$

Blood cells, erythrocytes and leukocytes, have a higher concentration of zinc than plasma

Functions

1 Zinc is essential for normal growth and sexual development

2 It is required for the synthesis of nucleic acids, which is essential for cell division and growth

3 In the form of zinc fingers, it is a constituent of some proteins which regulate transcription

Many enzymes require zinc for their catalytic activity

These include carbonic anhydrase, carboxypeptidase, lactate dehydrogenase, malate dehydrogenase, glutamate dehydrogenase, alcohol dehydrogenase, alkaline phosphatase etc

1 Zinc is present in the β -cells of the islets of Langerhans

2 It is required for the storage and release of insulin

Absorption

Zinc is absorbed from the small intestine

Copper, cadmium and calcium interfere with the absorption of zinc

Phytates also retard zinc absorption by forming an insoluble complex with zinc

Daily requirement

Age and sex	Requirement
Infants	5 mg/day
Children	10 mg/day
Adult men	15 mg/day
Adult women	12 mg/day
Pregnant women	15 mg/day
Lactating women	20 mg/day

Dietary sources

Zinc is widely distributed in foodstuffs

Liver, kidney, meat, fish, eggs, milk, yeast and whole grain cereals are good sources of zinc

Zinc deficiency

A dietary deficiency of zinc may occur in vegetarians taking refined wheat flour as their staple diet

It can also occur in acrodermatitis enteropathica

It causes retardation of growth, dwarfism, delayed puberty and hypogonadism

A milder deficiency may cause poor wound healing and impaired perception of taste

Cobalt

About one mg of cobalt is present in an average adult

It is distributed chiefly in liver, kidneys and bones

It is present almost entirely as a constituent of vitamin B₁₂

Inorganic cobalt is not known to perform any biological function in human beings

It functions solely as a component of vitamin B₁₂

It must be provided in the diet as vitamin B₁₂

Inorganic cobalt is not absorbed from the alimentary tract

Manganese

■ About 12-20 mg of manganese is present in an average adult

■ Liver, pancreas and kidneys contain relatively more manganese than other tissues

Manganese is present mainly in the mitochondria and nuclei of the cells

Manganese is absorbed from the small intestine

Less than 5% of the ingested manganese is normally absorbed

■ Manganese is required for:

- Formation of matrix of bones and cartilages
- Normal reproduction
- Normal functioning of central nervous system
- Stabilizing the structure of nucleic acids

□ A number of enzymes require manganese as a cofactor e.g.

- Superoxide dismutase
- Arginase
- Acetylcholine esterase
- RNA polymerase
- Carboxylases
- Glycosyl transferases

The daily manganese requirement is believed to be 2-5 mg

Whole-grain cereals, legumes, nuts, green vegetables and fruits are good sources of manganese

Molybdenum

Molybdenum is present in very small amounts in the human body, principally in liver and kidneys

It is a component of xanthine oxidase, aldehyde oxidase and sulphite oxidase

Sulphite oxidase converts sulphite and sulphur dioxide into sulphate

The exact requirement for molybdenum is unknown

An average diet provides 75-100 μg of molybdenum a day

Molybdenum deficiency is unknown in human being

Excessive intake of molybdenum may cause

Chromium

The total amount of chromium in an average adult is about 6 mg

It is widely distributed in the body

Chromium is a constituent of glucose tolerance factor (GTF) which binds to insulin and potentiates its actions

A relationship between chromium deficiency and glucose intolerance has been shown

The absorption of chromium is less than 1%

Stainless steel utensils contain chromium which can be absorbed

Chromium requirement is about 0.2 mg/day

Excess chromium can be toxic

Selenium

Selenium is present in human body in minute amounts

About 6 mg is present in an average adult

It is widely distributed in the body

Kidneys, liver, muscles, pancreas, pituitary and skin contain relatively more selenium

The role of selenium in the nutrition of animals has been known for sometime

It is involved in normal growth, reproductive functions and prevents hepatic necrosis and muscle dystrophy in several animal species

Its exact role in human beings is still being investigated

It may be involved in the synthesis of coenzyme Q

It is believed to play a role in immune response

It is a component of some proteins in the form of selenocysteine

The most definitive role of selenium, discovered so far, is in the prevention of peroxidation of lipids and other compounds

Hydrogen peroxide, formed in the tissues by the action of aerobic dehydrogenases and superoxide dismutase, is a toxic compound

It is detoxified by reduced glutathione



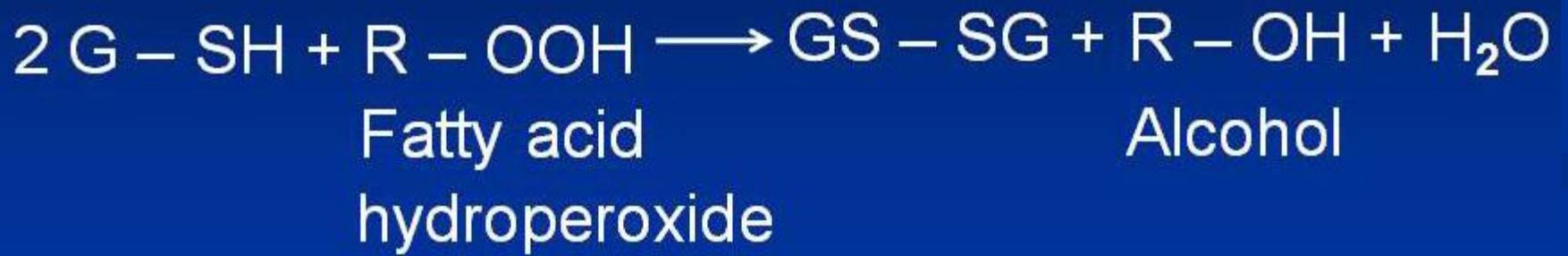
Reduced
glutathione

Oxidised
glutathione

This reaction is catalysed by glutathione
peroxidase

Selenium is a constituent of glutathione

Glutathione peroxidase can also detoxify fatty acid hydroperoxides (R-OOH) formed by the action of hydrogen peroxide on fatty acids



Thus, selenium acts as an anti-oxidant

It protects the tissues against the potentially toxic effects of hydrogen peroxide

Vitamin E also does the same but by a different mechanism

The selenium requirement is about:

- 70 $\mu\text{g}/\text{day}$ in adult men
- 55 $\mu\text{g}/\text{day}$ in adult women

Fluorine

About 2.6 gm of fluorine is normally present in the human body

More than 95% of it is present in bones and teeth

Fluorine is ingested in the form of fluorides

It is readily absorbed from the gut and enters the extracellular fluids

Fluoride makes the bones resistant to osteoporosis in later life

It makes the teeth resistant to dental caries

1 Certain bacteria, normally present in the oral cavity, act on dietary carbohydrates and convert them into lactic acid

2 Lactic acid corrodes the enamel of the teeth and produces cavities (dental caries)

3 Fluoride hardens the enamel, and makes it resistant to attack by lactic acid

Drinking water is the main source of fluoride

Seafood, cheese and tea may provide small amounts but other foods are generally poor in fluoride

The fluoride intake generally depends upon the fluoride content of water

In India, where water intake is relatively high, a fluoride content of 0.5-0.8 parts per million (ppm) in water will provide sufficient fluoride

If the fluoride content is less than this, dental caries may become a public health problem

In such areas, fluoride must be added to the drinking water (fluoridation) to raise its fluoride concentration to 0.5-0.8 ppm

Fluoride is potentially toxic

Excessive intake causes fluorosis which may be:

- Dental fluorosis
- Skeletal fluorosis

Fluorosis occurs when fluoride content of water exceeds 1.2 ppm or the daily fluoride intake exceeds 3 mg

In mild cases, only the teeth are affected (dental fluorosis)

The teeth become mottled and corroded

In severe cases, the bones are also affected
(skeletal fluorosis)

The bones of the vertebral column, pelvis and
limbs become deformed

Tendons and ligaments are calcified

Fluorosis occurs in those geographical areas where the fluoride content of water is high

Defluoridation of water is recommended in such areas to prevent fluorosis