UNIT 5

METALS IN BIOLOGICAL SYSTEM

Structure

5.1 INTRODUCTION

The last block had four units where you learnt about the important inorganic reagents, organometallic compounds alongwith their nomenclature and the metal carbonyl compounds. The applications of inorganic chemistry to living systems is one of the most rapidly developing areas in modern inorganic chemistry. There are vital “inorganic” links in the processes that are discussed in this block on bioinorganic chemistry. Of course, this interdisciplinary subject is still in its developmental stage and is very futuristic in nature. Scientists are still trying to find out the answers to many unsolved puzzles of the living system. In this unit you will be studying about metals in biological system in details.

Expected Learning Outcomes

After studying this unit you should be able to:

- ❖ understand the importance of bioinorganic chemistry;
- ❖ appreciate the presence of metals & non-metals in biological system; and
- ❖ define the essential, non-essential, trace & toxic metals.

5.2 BIOINORGANIC CHEMISTRY

Bioinorganic chemistry involves the interface of inorganic chemistry and biology. The term "inorganic biochemistry" or "bioinorganic chemistry" is used in the latter part of the twentieth century which includes studies on the biological functions of typically "inorganic elements", – the metals in particular. Many inorganic elements are essential to life processes. Different elements are taken up selectively by different cells and other components inside the cells, and utilized. The basics of coordination chemistry have been discussed in Units 4 and 5 of BCHCT 137 which you may recapitulate before reading this unit. Here you will be discussing the functions of the metals in the biological environment in context with the coordination chemistry which you may have learnt earlier. The mystery of living systems have always attracted scientists who tried to unravel it with the help of experimental research. In this process, model compounds with structures almost the same as in living systems have been tried to find the mechanism of reactions in natural systems. The term "bioinorganic" obviously has lot of contradictions. The source of this are the misconceptions that have been there when modern science evolved. In the early 19th century, chemistry was still divided into "organic" chemistry which comprised of substances which were found in "organisms", and an "inorganic" chemistry which comprised of "dead matter". But then in 1828, synthesis of "organic" urea from "inorganic" ammonium cyanate (NH_4OCN) changed the basis of this terminology.

By 1960, bioinorganic chemistry became an independent and highly interdisciplinary research area.

Sophisticated and advanced analytical techniques have revealed that apart from carbon many metals and non-metals are present in biochemical processes and they are important for life. Even trace elements could be detected in these processes. Thus we can say that bioinorganic chemistry is mainly the study of the function of inorganic substances in living systems, alongwith the transport, speciation and thereby, mineralization of inorganic materials and their use in mechanical therapy and diagnosis.

The major areas of study of bioinorganic chemistry may be broadly identified as :

(i) biological functions of different elements which are mostly known to form inorganic compounds;

(ii) to find out if these elements and their compounds are toxic and how to overcome the toxic effects;

(iii) metal ion transport and storage in living systems;

(iv) use of metals as probes and drugs;

(v) artificial fixation of nitrogen and other applications.

The following two chemical processes involved in the chemistry of life in which metal ions play an active role are:

(i) Using solar energy to facilitate chemical reactions that produce oxygen and reduced organic compounds from carbon dioxide and water (photosynthesis)

(ii) Oxidation of organic matter to produce carbon dioxide, water and energy (respiration).

The “reaction flask” of living organisms is the cell. Each cell is characterized by an outer membrane whose function is to contain a highly organized chemical system and to monitor the influx of needed reagents. Within the cell membrane are several organelles immersed in cellular fluid, cytoplasm. Two of these organelles, the nucleus and mitochondria, are the focus of most of the chemistry. The nucleus is surrounded by a nuclear membrane, within which occur the process concerned with DNA-DNA replication, RNA synthesis and membrane synthesis. The other important organelles are the mitochondria within which occur the redox/electron transfer processes important in the combustion of glucose and synthesis of ATP. In animals the mitochondria are the sole centres of energy generation in the cell. The cells of green plants contain in addition chloroplasts which contain chlorophyll. This chlorophyll only enables the light sensitized phosphorylation reaction associated with ATP generation.

DNA is deoxyribose nucleic acid RNA is ribose nucleic acid. ATP is adenosine triphosphate.

In the dark, the mitochondria of plant cells maintain this regeneration though at a lower rate than in animals. This is because in green plant cells it is rarely found. The other organelles are lysosomes and golgi bodies involved in digestion and excretion respectively. The endoplasmic reticulum is an intracellular network of channels for transport of proteins synthesised by ribosomes that surround the surface of the channels.

An important feature of living systems is their unique dependence upon kinetic stability for their existence. Organisms must maintain steady states far from equilibrium by a continuous flow of nutrients and energy in a variable environment. All are thermodynamically unstable. They would burn up immediately to carbon dioxide and water if the system came to thermodynamic equilibrium. Thus to a living organism reaching equilibrium is equivalent to death. Life processes depend upon the ability to restrict these thermodynamic tendencies and allow kinetics to control and produce energy as needed. So, apart from capturing solar energy, it is important to use catalysts to release that energy in controlled manner. Examples of such catalysts are enzymes which control the synthesis and degradation of biologically important molecules. Metal ions play a crucial role for the activity of those enzymes. Metal containing compounds are also important in the process of chemical and energy transfer, reactions involving transport of oxygen to the site of oxidation and various redox reactions. Most of the reactions for obtaining energy for living systems are basically inorganic. The reactions are mediated and made possible by complex biochemical processes.

Inorganic elements can also be artificially introduced to the living system in diagnostic techniques like barium meal X-ray, MRI (Magnetic resonance imaging, suitable for paramagnetic metal ion) and as medicines e.g., platinum complexes in oncology, gold complexes in arthiritis and lithium salts as antidepressants. In these ways, bioinorganic chemistry provides many interesting insights about the functions of inorganic substances in living systems. In the next section you are going to study about the metals and non-metals in biological system.

Before moving to the next section, please try to solve the following SAQ.

SAQ 1

Give any two major areas of study of bioinorganic chemistry.

5.3 METALS & NON-METALS IN BIOLOGICAL SYSTEM

In this section you are going to study the metals and non-metals in biological system.

5.3.1 Essential, Non-essential Elements

Now let us discuss the essential elements in biological systems.

Essential elements are those elements which have a specific role indispensable to sustain life in a living organism. The normal functioning of the living system will suffer if there is absence or even deficiency of the element.

About thirty elements appear essential to some form of life (Table 5.1). The most abundant biological element is hydrogen which constitutes 63% of the atoms in a human body. Next comes oxygen (25 .5%), carbon (9.5%) and nitrogen (1.4%). The following seven elements in order of their abundance in humans are Ca, P, Na, K, S, Cl and Mg; together they constitute about 0.6%.

Table 5.1: Essential elements in living organisms

bulk elements : □; others are trace elements

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
[H]												B	C	[N]	[O]	[F]
[Na]	[Mg]												Si	P	[S]	[Cl]
[K]	[Ca]			V	Cr	Mn	Fe	Co	Ni	Cu	Zn			As	Se	Br
					Mo								Sn			I
					W											

There are nearly 40 elements in the periodic table which are biologically active. Any species responding to or involved in a biological system is termed biologically active. The heaviest biologically active metals and non-metals are molybdenum and iodine whilst the lightest counterparts are lithium and hydrogen. The following elements are essential of human life.

Metals: Na, Ca, Mg, V, Cr, Mn, Fe, Co, Cu, Zn, Mo, Sn.

Non metals: H, C, N, O, P, S, Se, F, Cl, Br, I.

The 11 most abundant elements are H, O, C, N, Na, K, Ca, Mg, P, S, Cl; the next seven are less abundant - Mn, Fe, Co, Cu, Zn, Mo and I whilst the remainder occur in ultratraces. The amount of these elements present in a 70 kg man are shown in Table 5.2 below.

Table 5.2: Amounts of essential elements present in a 70 kg man

Oxygen - 45.5 kg	Ca – 1050 g
Carbon – 12.6 kg	K – 140 g
Hydrogen – 7 kg	Na – 105 g
Nitrogen – 2.1 kg	Mg – 35 g
Phosphorus – 700 g	Fe – 4.2 g
	Zn – 2.3
	Mn, Cr, Mo, Co, Cu < 1g
	Eg. Cu – 0.11 g
	Mn – 0.02 g

Hydrogen, oxygen and carbon are present in water, carbohydrates, proteins etc. Nitrogen is an essential constituent of proteins. Phosphorus is present in ATP, ADP, DNA, RNA, bones, teeth etc. Sulphur is present in some amino acids and vitamins. Sodium, potassium, magnesium, chlorine are present in body fluids and cytoplasm. Sodium ion (Na^+) is the major component of extracellular fluid and potassium (K^+) of intracellular fluid. Together they act as charge carriers and are involved in osmotic balance. That is, they maintain a constant osmotic pressure on either side of cell membrane. The acid-base equilibrium is maintained by them. They also control sensitivity of nerves and muscles along with calcium ions (Ca^{2+}) and magnesium ions (Mg^{2+}). Calcium is required for bones and teeth and maintain correct rhythm of heart beat and converts fibrinogen to fibrin. It also stabilises protein structure. Mg^{2+} are found complexed with nucleic acids and are necessary for nerve-impulse transmission. All the phosphate transfer enzymes need Mg^{2+}. It is also an essential constituent of chlorophyll.

Manganese (Mn) and cobalt (Co) are present in enzymes, for example, arginase involved degradation of protein. Co is present in Vitamin B_{12}. Copper (Cu) is a constituent of metalloenzymes involved in electron transfer. Iron (Fe) is present in hemoglobin, myoglobin, cytochromes which act as O_2 carrier, O_2 storehouse and electron transfer respectively. Zinc (Zn) is present in enzymes particularly hydrolases and in insulin. Molybdenum (Mo) helps in nitrogen fixation in plants while iodine (I) is involved for proper functioning of thyroid gland.

We may classify the elements in a way that suggests their function in the complex dynamic system of a living cell. Let us now discuss a system that classifies elements according to their occurrence in three different biological environments.

- Firstly, it may be in the extracullar fluids and outer wall of cell-membrane – Na, Ca, Cu, Mo, Cl, Al.
- Secondly, it may be inside the cell, starting from inner wall of cell membrane in the aqueous phase known as cytoplasmic fluid - K, Mg, Co, Zn, P, S
- Also it may be present organelles inside the cell – K, Mg, Fe, Co, Zn, Mn, P, S

However, this classification is not very rigid.

Next, let us dscuss the classification of the elements on the basis of mechanism of action as:

- Essential elements: they are absolutely necessary for life processes and are needed in large quantites e.g. O, C, H, N, P, Na, K, Mg, Cl, Ca, S
- Trace elements: these are essential but are present in trace amounts - I, Fe, Cu, Zn, Co, Mn, Mo.
- Non-essential: they may be present in biosystem, but in their absence other elements may serve the same purpose e.g. Al, Ba, Sn, Sr.
- Toxic: they disturb the normal function of biological system e.g. Hg, Pb, Cd, As etc.

Next let us understand what are biomolecules. Biomolecules containing one or more metallic elements are called metallo biomolecules. These are natural products and usually complex coordination compounds, whose active sites are involved in different processes e.g., electron transfer, O_2 transfer, catalysis etc. Most biochemical processes are related to the chemistry of hydrogen and elements of the second and third periods of the periodic table. Every cell (animal, plant, microbial) contain the same elements in the same proportion. Six nonmetals (H, C, N, O, P, S) provide the structural elements to the protoplasm. The relative geochemical abundance and intrinsic chemical properties like, (i) small atomic radius, (ii) catenation, (iii) ability to from multiple bonds of these six elements suggest their unique suitability for building blocks of life. Table 5.3 gives an idea of the important metallobiomolecules

Table 5.3: Some representative examples of different metallobimolecules

METALLOBIOMOLECULES

- METALLOPROTEINS
  - Transport and Storage
    - *Electron transport*
      - Cytochromes (Fe)
      - Iron-sulphur (Fe)
      - Copper blue (Cu)
    - *Dioxygen management*
      - Haemoglobin (Fe)
      - Myoglobin (Fe)
      - Haemerythrin (Fe)
      - Haemocyanin (Cu)
    - *Metal management*
      - Ferritin (Fe)
      - Transferrin (Fe)
      - Ceruloplasmin (Cu)
  - Metalloenzymes
    - *Hydrolases*
      - Phosphates (Mg, Zn, Cu)
      - Aminopeptidases (Mg, Zn)
      - Carboxypeptidases (Zn)
    - *Oxidoreductases*
      - Oxidases (Fe, Cu)
      - Reductases (Fe, Cu, Mo)
      - Superoxide dismutases (Fe, Cu, Mn)
    - *Isomerases and synthetases*
      - Vitamin B_{12} coenzyme (Co)
    - *Transferases*
      - Kinases (Mg)
    - *Lyases*
      - Enolases (Mg)
    - *Ligases*
      - Glutamine synthetase (Mg, Mn)
- NON-PROTEINS
  - *Metal storage and transfer*
    - Siderophores (Fe)
  - *Photoredox*
    - Chlorophyll (Mg)

The number of elements that are biologically important comprises a relative small fraction of the known elements. Geochemical abundance is an important parameter. All essential elements are abundant in the earth's crust. Four elements, Al, Si, Ti, Zr are abundant but not essential because at biological pH they form insoluble oxides. They also form very weak complexes with biological species. Natural abundance limits availability of elements for use in biosystem. The metals for importance in enzymes are mainly those of the first transition series and other elements of importance are relatively the light ones. Natural abundance of elements decreases with increase in atomic number. The heavier elements are not very important as far as biological activity is concerned. The conclusion is inescapable "Life evolved utilizing elements that are abundant and available to it and became dependent upon them". The rarer elements were not used by living systems because they were not available; neither did the system evolve mechanisms to cope with them. They were later introduced to the environment and ecosystem by human activities.

Most of essential metals except Na, K cannot occur in the biosystem in the free state as under the prevailing pH conditions they get hydrolysed and precipitated. They must be present and transported as complexes. Most of the essential and trace metals are transition metals which are capable of forming complexes and chelates with species like citrate, tartrate, lactate, amino acids present in the plasma. Many metal complexes of biological macromolecules have been isolated in the free state for example hemoglobin, myoglobin, cyanocobalamine, chlorophyll a, cytochrome-c etc. The presence of others or their formation as intermediate products taking part in metabolic processes of living system has been inferred from a catalytic study of enzymes.

A successful organism must have a subtle command over a complex pattern of reactions that proceed at high but controlled rates. Loss of this control leads to the organism's disease and death. Life depends on how these reactions are controlled and thus the role of catalysts is important. These catalysts are enzymes which are polypeptides i.e. macromolecules, formed from α-amino acids linked by a peptide bond $-\overset{\overset{\displaystyle O}{||}}{C}-\overset{\overset{\displaystyle H}{|}}{N}-$. The term "peptide residue" denotes that part of the amino acid that remains in the chain once the peptide link is formed by elimination of H_2O. Enzymes are named according to the reactions they catalyze e.g. hydrolase, oxidase, reductase etc.

The naturally occurring amino acids have different side chains eg. alkyls,-COOH, $-NH_2$, -OH, -SH. These functional groups confer hydrophobic and hydrophilic character, Bronsted acidity/basicity, Lewis acidity to complex with a metal. About 30% enzymes are metalloenzymes having a metal atom as the active site. The functional groups modify the immediate environment. The protein part of the enzyme is called apoenzyme and the non-protein part, the prosthetic group. Enzymes not only control the rate of a reaction but by favouring certain geometries in the Transition State (TS) can lower the activation energy to favour the formation of the desired product. Metal ions also occur in transport and storage proteins and in non-protein complexes.

Life originally appeared on earth in an overall reducing atmosphere. As shown by Miller and Urey (1953), lightning discharges through a mixture of methane, water, ammonia and hydrogen to produce significant amounts of amino acids essential to life processes. Abelson and others later showed (1960s) that solar ultra violet radiation not filtered by the earth's ozonosphere acts on a mixture of carbon monoxide, carbondioxide, nitrogen and a small amount of hydrogen producing, among others, hydrogen cyanide. This molecule can subsequently give rise to glycine, adenine, and other biologically significant molecules. These compounds, formed in the primitive earth, might have undergone a series of complex chemical evolution over millions of years to produce living organisms which could replicate themselves and undergo biological evolutions (nearly 3.5 billion years ago). Photosynthetic organisms appeared approximately 2.5 billion years ago when the atmosphere became gradually rich in oxygen and ultimately sustained aerobic forms of life. The diverse biological world of today has largely developed with this form of life and is a unique example of nature's delicate balance between constructive and destructive oxidation by oxygen. The amazingly complex and yet precisely synchronized biological processes involve, in addition to H, C, N, O, and P, other elements abundant on the earth, particularly a large number of metals, in both bulk and in trace. As more and more finer details regarding these roles get unveiled, the emphasis on a particular area of study generates new terminologies to justify the thrust area.

5.3.2 Trace & Toxic Metals

The living system also requires small amounts of other elements as shown in Table 5.2. The requirement of these elements may be very low (i.e., 10^{-4} g mole or less in a 75 kg adult) or moderate (e.g., 10^{-1} g mole). All these elements are classed as essential trace elements of which in top priority; iron, copper and zinc. Elements present in exceedingly small amounts are called ultra-trace elements, for example, Mn, Mo, Co, Ni and V.

Hydrogen are involved in the biological system and the *s*-block elements sodium, magnesium, copper and calcium. Na, K, Ca and Mg, are the most abundant metal ions in living systems. They occur at fairly high concentration in most cells and constitute 99% of the metal content (more than 1% of the body weight) in man.

Hydrogen

It is the most abundant element in the biosphere. The small atoms can effectively “seal” the residual valences of carbon, nitrogen, and oxygen without any structural strain. When bonded to nitrogen and oxygen, hydrogen can form hydrogen bond; these weak but extensive bonds are crucial in stabilizing many biological systems, for example, the double helix of DNA. The weakness of the bonds is an advantage in such systems since the helix must unwind during replication. The life supporting properties of water and many other functions like operations of several enzyme are also dependent on hydrogen bond.

Sodium and Potassium

In spite of their established chemical similarity, the elements differ in their ability to penetrate cell membranes presumably due to their different ionic size. The metals also differ in their transport mechanism and efficiency to activate enzymes. Sodium ions are more abundant outside the cells, for example in the blood plasma and in the extracellular fluid surrounding the cells. They participate in transmitting nerve signals and regulate the flow of water across cell membranes. The transport of sugars and amino acids into cells is also influenced by sodium ions (Na^+).

On the other hand, potassium ions occur at a higher concentration inside cells. They also activate many enzymes and participate in the oxidation of glucose to produce ATP. Both sodium and potassium ions are also involved in the transmission of nerve signals.

Magnesium

The involvement of magnesium in photosynthesis by plants is well-known. Magnesium is also an essential element for animal physiology. The major portion of magnesium is an adult human is in the skeleton while the rest is inside the cells. The Mg^{2+} ion in cells is the next most important cation after K^+. The small doubly charged cation has a high charge/size ratio and is strongly hydrated - mostly to $[Mg(H_2O)_6]^{2+}$ which binds the $ROPO_3H$ – groups in nucleotides (ATP, ADP) and polynucleotides (DNA, RNA). The ion may form strong complexes with oxygens on various phosphate groups; such complexes appear to be important in storing energy and use of the same when necessary. All enzymes utilizing ATP in phosphate transfer require Mg^{2+} as cofactor.

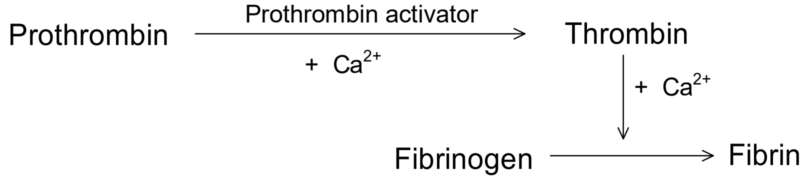
Intracellular magnesium ions are also essential to keep ribosomes intact. Ribosomes are RNA-protein complexes of particle size of about 20,000 pm diameter which occur in the cytoplasm and function as sites for protein synthesis.

Calcium

It is the major constituent of bones and teeth. It is also important in neuromuscular function, interneuronal transmission, maintenance of cell membrane integrity and blood coagulation. The calcium present in bones gets continuously solubilized and redeposited in our body to the extent of about 400 mg per day. The concentration of calcium ions (Ca^{2+}) in plasma is closely maintained around 100 mg/L by means of two hormones namely, calcitonin and parathyroid hormone. Together they help in building and mobilising bone structure.

During the period of growth, deposition of bone must exceed resorption. With ageing, resorption predominates and causes loss of about 15-30 mg per day. Vitamin D promotes deposition of bone. This vitamin is synthesized by the action of ultra violet light on 7-dehydrocholesterol. So inadequate exposure to sunlight may result in diseases of the bone like ricket in childhood and softening of bones (osteomalacia) in later life.

Calcium ions in the cytoplasm of muscle fibres play an important regulatory role in muscle functioning. Clotting of blood is also influenced by the presence of Ca^{2+} ions. Blood contains prothrombin, a soluble protein. This is converted to the enzyme thrombin by the action of prothrombin activator in the presence of Ca^{2+} ion. Thrombin, again aided by Ca^{2+}, now clots the blood by converting its soluble fibrinogen into insoluble fibrin as shown below:



It is interesting to note that the distribution of essential elements in the biosphere is not in harmony with the abundance of the elements in the earth's crust. About 88% of the earth's crust is made from the four most abundant elements oxygen, silicon, aluminium and iron. In living cells, more than 98% is derived from the four elements hydrogen, carbon, nitrogen and oxygen. On the other hand, the concentrations of different ions in sea-water show a similarities with those in living systems, for example, the blood plasma. Thus life probably originated in the sea and evolved thereafter. The process of evolution continued with the relatively abundant elements which were found suitable for sustained development of the process. The metal ions chosen were able to form thermodynamically stable units in the active centres of proteins (metalloproteins) or other biomolecules. At the same time, they had to be kinetically labile, be able to assemble and disassemble very fast under physiological conditions. Titanium and zirconium, in spite of their high abundance, are not found in living cells as the metals are readily precipitated as insoluble hydrated oxides at our body pH. Also the metals have a uniform high +4 oxidation state unsuitable for reversible electron transfer and other reversible biological processes.

The health response of an organism to an essential element follows the general type of curve shown in Fig. 5.1; details of the curve vary from one element to another. At and around zero intake of the element, the condition may be anything between bare survival to death. As the dose is slowly increased, the organism gradually reaches a stage of smooth functioning. But an excessive dose will gradually result in toxicity by the same element and ultimately lead to death. For some elements, the safe dose and the toxic dose may be quite close, for example 50 to 200 μg for selenium (Table 5.4).

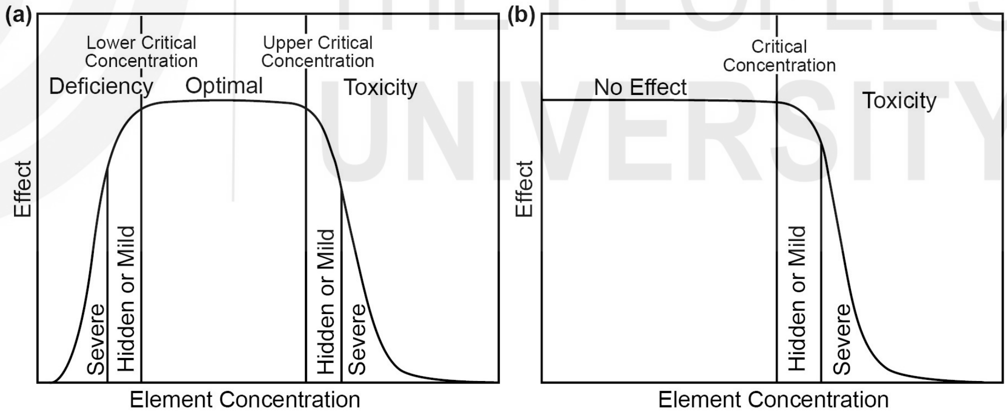


Fig. 5.2: Nature of variation of response to increasing dose of an essential element.

Table 5.4: Recommended daily doses of some elements for an adult human being (~70 kg)

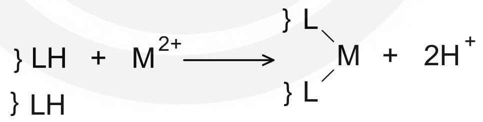
Element	Intake (per day)	Element	Intake (per day)
Iron	10 mg (male)	Fluorine	1.5-4.0 mg
	18 mg (female)	Molybdenum	150-500 μg
Zinc	15 mg	Iodine	150 μg
Manganese	2.5-5.0 mg	Chromium	50-200 μg
Copper	2.0-3.0 mg	Selenium	50-200 μg

Deficiency or excess of these elements may give rise to metabolic disorders, inhibited growth and other diseases.

Sometimes one element strongly interferes with the uptake of another element an this is known as antagonism. The copper containing enzyme monoamine oxidase is involved in the cross-linking of polypeptide chains responsible for structural strength of arteries. As a consequence, copper deficiency in herbivorous animals causes anemia, loss of pigmentation and ultimately death owing to arterial lesions. However, even when the animals are supplied with pasture having a plentiful supply of copper, the take may be still hampered if the soil contains a high level of molybdenum – presumably owing to the formation of highly insoluble copper thiomolybdate in the gut.

Let us look into specific examples of toxicity of metal ion in biochemical system. Metal ions are essential for life processes only in limited quantity. The concentration of the essential metal ions inside the cell is controlled by enzyme regulated transport mechanisms and excess unused metal ion is ejected. The biosystem does not have transport mechanism for some (impurity) elements and these cause disorder. Such metal ions are toxic, the highly toxic ones are generally heavy metals of second and third transition series (soft acids) and metalloids like arsenic. Toxicity is of two types, namely chronic toxicity and acute toxicity. Chronic toxicity arises due to high rate of turnover of metal ion in the body. Whenever metal ions are in excess in the body, they are stored in specific sites to a limited extent and the excess metal ion interferes in body processes. Acute toxicity arises due to certain chemical activity like deactivation of enzymes and other biomolecules. Let us understand this in detail now.

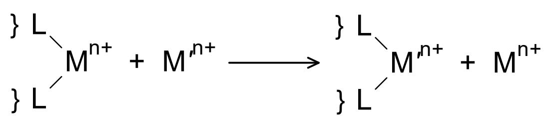
(i) The metal may get bound to coordinating site of the enzymes, which are binding sites of essential metal ions. Thereafter the essential biological function of the enzyme is lost resulting in its deactivation



L = O, N, S

Enzyme

(ii) Deactivation of an enzyme can be due to displacement of metal ion present in the enzyme, which is essential for its catalytic activity by a toxic metal ion e.g. replacement of Zn^{2+} by Pb^{2+}, Cd^{2+}, Hg^{2+}.



As the external metal ion is not biochemically active, the activity of the enzyme is lost. Common example is Cd^{2+} replacing Zn^{2+}.

(iii) There may be cases when the external metal ion may change conformation of biomolecule and hence its biological activity.

(iv) The metal ion can get bound to DNA causing a change in base sequence, leading to transmission of wrong genetic information from

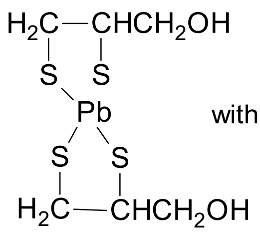
DNA which produces faulty protein and enzymes. This may give rise to birth defects too.

(v) The metal ion can bind to DNA stimulating its replication resulting in uncontrolled cell growth i.e., formation of malignant tumours.

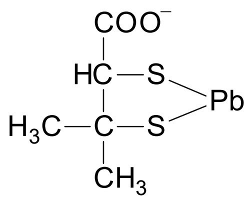
Lead

This enters the biosystem through food, water and air. Lead pollution can be caused by factories, particularly those manufacturing batteries. The antiknock compound $Pb(Et)_4$, namely tetraethyl lead used earlier in gasoline was present in exhaust gases of automobiles and was a source of lead (Pb) in the atmosphere. Lead is also present in paints and pigments. Lead gets deposited in the softer tissues and passes to the blood stream. Pb^{2+} has strong affinity for the –SH group of enzymes and hence gets bound to these and deactivates them. The principal indicators of lead level in human beings is lead in blood expressed as μg/mL or μmol/L. At concentration as low as 10 μg/mL it inhibits some enzymes when the concentration becomes higher, it affects digestive, muscular, nervous and other organs. Lead affects the biosynthesis of bones as Pb^{2+} replaces Ca^{2+} in bone. Deposition of lead in brain results to irreversible brain damage. Lead also damages kidney, liver and intestinal tract.

The major biochemical effect has been attributed to its influence with heme synthesis giving rise to hematological damage. It lowers the formation of δ-aminolevulinic acid (ALA) and its conversion to porphobilinogen is inhibited. Lead deactivates the enzyme ALA dehydrase and overall effect is disruption of synthesis of hemoglobin, other respiratory pigments and cyctochromes. Thereby deficiency of hemoglobin leads to anemia. Methods for removal of lead from the body depend on formation of coordination compounds which are excreted. Common antidotes are calcium sodium salt of EDTA ($CaNa_2EDTA$), succimer (Dimethyl succinic acid or DMSA), 2,3-dimercapto-1-propanol (British anti-Lewisite (BAL) and d-penicillamine. The probable coordination compounds of lead ions with some antidotes are shown below;



with BAL



with d-penicillanine

Arsenic

Arsenic (As) poisoning is caused through air and water (mainly ground water) pollution. Elemental arsenic is not absorbed through the intenstinal wall and is not toxic. As(III) is more toxic then As(V). Poisoning causes gastroenteritis, skin lesion and skin cancer. As(III) shows toxicity due to binding with the –SH group of the enzyme pyruvate dehydrogenase, which is essential for ATP synthesis. At higher concentration. As(III) causes coagulation of proteins probably by binding to –SH group of the proteins. It also binds to the protein keratin in the hair affecting its texture.

Excess arsenic affects the biosynthesis of ATP in another way. It is chemically similar to phosphorus and interferes in stepwise synthesis of ATP. In presence of AsO_3^{3-}, phosphorylation of glyceraldehyde-3-phosphate to give 1,3-disphosphoglycerate does not occur, rather 1-arseno-3-phosphoglycerate is formed and further oxidative phosphorylation leading to ATP formation does not occur. The main biochemical actions of arsenic are as follows:

- deactivation of enzymes e.g. pyruvate dehydrohenase system, citric acid cycle is also inhibited apart from others;
- coagulation of protein; and
- uncoupling of phosphorylation.

DMSA is dimethyl succinic acid.

A lethal dose of the more toxic form of arsenic is 125 mg/kg body weight but for less toxic forms it is upto 200 mg/kg body weight. The major antidotes for arsenic poisoning include chemicals having –SH groups which can bind to arsenic forming chelate e.g. (British anti-Lewisite (BAL), succimer (DMSA).

Cadmium

Cadmium (Cd) is a very toxic metal with a lethal dose of greater than 350 mg at a time. It enters the body system through the food chain (40 mg/day) and industrial fumes. Tobacco contains nearly 1μg Cd/g. Thus nearly 2-4 μg of Cd are inhaled per packet of cigarette. This is the major source of inhaled Cd. 25-50% of inhaled Cd is absorbed into the body while the absorption from food is almost 6%. Other sources of Cd are from plating, pigment and battery manufacturing industries. Inhaling Cd laden dust leads to respiratory problem. Cd accumulates in liver and kidneys and may produce irreversible damage. Certain compounds of Cd are carcinogenic. The main disease associated with Cd poisoning is Itai-Itai disease which was observed in the Jinzu river basin (Japan). This water was used for irrigation and patients developed this disease after eating rice grown on fields irrigated with this water. The disease is associated with brittle or hollow bones, high rate of fracture, osteoporosis and intense bone-associated pain. It is very interesting to note that Cd cannot pass through the placental membrane and thus cannot harm new born babies. Excess Cd can displace Zn from enzymes and deactivate them causing metabolic disorders. Regular intake of Zn provides protection against Cd poisoning.

The average amount of Cd accumulated in the body over a life time is nearly 30 mg. Metallothioneins (MTs) are low molecular weight cadmium binding proteins present in animal and human tissues. The deposited Cd is taken up by MTs and Cd binds to its –SH group thereby getting trapped and its toxicity controlled. The protein bound Cd gets accumulated in the kidneys and damages them. Long-term cadmium exposure gives rise to kidney or bone disease, reproductive toxicity and cancer in animals and human. Its antidotes are (British anti-Lewisite (BAL) and $CaNa_2EDTA$.

Mercury

Mercury (Hg) is the most toxic heavy metal and may enter the biological system as Hg vapour, mercury salts or alkyl/aryl mercury compounds. The major source is industrial processes involving mercury compounds and organomercurials used as fungicides. Upto 80% of Hg may be absorbed depending on its chemical form. The methyl mercury compounds are most extensively absorbed while for inorganic mercury compounds the absorption is nearly 15% mercury in blood and hair can be used for estimating the body burden. A blood Hg level of 20 μg/100 mL corresponds to a daily consumption of 200-300 μg of Hg. The distribution of mercury in different organs follow the order liver, kidney, brain, heart, lungs. Its presence is least in the muscles.

The toxicity of Hg depends on its chemical form. In the liquid form it is not absorbed by the human systems and is not toxic. However Hg vapours is absorbed into the blood and enter the brain. Hg(II) is toxic but cannot enter the cell as it cannot pass through the membrane. Hg(I) forms and insoluble chloride with gastric juice in stomach and is not highly toxic. However Hg(I) can enter the cell and get oxidized to Hg(II) and show high toxicity. Hg(II) like Cd(II) and Pb(II) has affinity for –SH group of enzymes as well as proteins and can deactivate them. It also inhibits the synthesis of δ aminolevulinic acid by deactivating specific enzymes and thereby decreases synthesis of heme. It can also form bonds with heme and serum albumin. The most toxic species are the organomercurials headed by methyl mercury (CH_3Hg^+). Mercury salts are converted into methylmercury in the biochemical system by the action of Vit B_{12}. The Co–C bond in Vit B_{12} is weak and can be readily transferred to the substrate causing alkylation. This methylmercury is taken up by aquatic plants and fish and finally enters animals and human bodies. The higher toxicity of organomercurials is due to their nonpolar nature, this makes them fat soluble and they readily pass through the biological membrane and spread all over the body. The Hg–C bond does not break easily hence CH_3Hg^+ is not excreted and retained in kidneys, brain, heart and muscles. CH_3Hg^+ can penetrate through the placenta and get accumulated in foetal tissue. Methylmercury gets attached to the cell membrane and hence the transport of sugar through the membrane is lowered whereas external passage of potassium ions (K^+) is increased. Thus the brain cells do not get sufficient energy and K^+–controlled nerve impulse transmission is impaired leading to tumours and mental instability. Such effects are observed distinctly when the concentration of mercury in the brain exceeds 20 μg/g. The effect is more serious in babies. It may cause irreversible damage to central nervous system is irreversible leading to cerebral palsy, mental retardation and convulsions. CH_3Hg^+ poisoning also gives rise to segregation of chromosomes, chromosome breakage in cells and inhibited cell division.

The toxic effect of mercury was first realized when 121 persons in Japan were affected by a disease causing tremors and mental imbalance. They were residents near the Minamata bay where the effluents of the factory containing mercury compounds and CH_3Hg^+ was discharged. Though the concentration of CH_3Hg^+ was low it got accumulated in significant concentration in fish. People eating the fish were seriously affected and many babies were born with cerebral defects and this was referred as Minamata disaster.

So in this section you have learnt all about the metals and non metals in biological system. Before moving to the next section, please try to solve the following SAQ.

SAQ 2

What are the roles of sodium and potassium metals in biological system?

5.4 SUMMARY

In this unit, we first discussed the importance of bioinorganic chemistry. Then the different metals and non-metals in biological system along with the essential, non-essential, trace & toxic metals have been taken up. These will help you to understand the role of various metals in the biological system. In the next unit we will talk about the functions of *s*-block metals.

5.5 TERMINAL QUESTIONS

1. What is bioinorganic chemistry?

2. What is the role of manganese and cobalt in biological system?

3. Which metal ion has role in blood clotting and how does it do so?

5.6 ANSWERS

Self Assessment Questions

1. Any two areas may be given (from section 5.2)

2. The elements are similar chemically but differ in their ability to penetrate cell membranes presumably due to their different ionic size. They also differ in their transport mechanism and efficiency to activate enzymes. Sodium ions are more abundant outside the cells, (blood plasma and in the interstitial fluid surrounding the cells). They participate in transmitting nerve signals and regulate the flow of water across cell membranes. The transport of sugars and amino acids into cells is also influenced by Na^+ ions.

   But potassium ions occur at a higher concentration inside cells. They also activate many enzymes and participate in the oxidation of glucose to produce ATP. With sodium, K^+ ions are also involved in the transmission of nerve signals.

Terminal Questions

1. Bioinorganic chemistry involves the study and function of inorganic substances in living systems. It also deals with the transport, speciation and mineralization of inorganic materials and their use in mechanical therapy and diagnosis.

2. Manganese and cobalt are present in enzymes. The enzyme arginase have these metals and it has role in protein degradation. Co is present in Vitamin B_{12}.

3. Calcium ions play an important role in clotting of blood. Blood contains prothrombin, a soluble protein. This is converted to the enzyme thrombin by the action of prothrombin activator in the presence of Ca^{2+} ion. Thrombin, again aided by Ca^{2+}, now clots the blood by converting its soluble fibrinogen into insoluble fibrin.