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Review
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ESSENTIAL METAL CO-ORDINATION IN BIOCHEMISTRY

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The basic functions of essential metals are described. The metals are classified into two groups: mobile (ionic) and transition series metals. In the first group only calcium and magnesium are briefly discussed. For the metals of the transition series, the main biochemical functions are listed. Chromium is discussed at length. The main characteristics of manganese, iron, cobalt, nickel, copper, zinc, vanadium and molybdenum are listed. The significance of certain interactions is stressed.

Currently 25 elements of the periodic table are considered important for the existence and maintenance of life. Out of these, 12 are non-metals and 13 are metals (Table 1) (1, 2). These elements are either involved in vital biological functions or are constituents of biomolecules. For example, transition series metals even though they are present in only trace amounts, generally appear in the active centres of the enzymes, co-enzymes and other biological constituents which are responsible for the synthesis of aggregate molecules and their breakdown to bring about the normal functions of the body (3, 4).

The essential metals whose essentialities are well established may be classified into two broad groups; the main group of ions which are ionic and mobile (sodium, potassium, magnesium and calcium) and the transition series metals (vanadium, chromium, molybdenum, manganese, iron, cobalt, nickel, copper and zinc) which are covalently bonded or co-ordinated to some electron donor bioligand (5, 6). Each metal has its specific functions and the optimum metal ion concentration for such functions is homeostatically controlled (7, 8). It is important to determine not only the total amount of such metal but also the species present as this affects its bioavailability (9).

METALS OF THE MAIN GROUP

The main group metals may occur in compact mass such as in bones, teeth and in solution such as blood stream. While sodium and calcium occur outside the cell, potassium and magnesium are the main cations inside the cell and there exists an active ion pump mechanism for chemically pushing these in the direction according to the functional need in the system. Sodium and potassium are responsible for various biological functions such as maintenance of osmotic pressure and transmission of nerve impulses. Calcium controls the matrix in the bone and teeth and helps in precipitating milk casein, maintaining the normal heart rhythm and converting fibrogen into fibrin. However, insolubility of calcium compounds sometimes causes problems e.g. calcium oxalate, phosphate and/or carbonate readily precipitate in the blood stream which becomes oversaturated with calcium. Ageing encourages such precipitation in the form of gall bladder stones, cataracts and hardening of soft tissues. A Ca^{2+} metalloprotein containing twelve lysyl amino groups and a free amino terminus has been found in bovine α-lactalbumin; all the amino groups can be ^{13}C dimethylated without altering Ca^{2+} binding or biological activity (10).

Magnesium has a very important role in oxidative phosphorylation, a process that occurs in mitochondrial membrane to produce main fuel of life-adenosine triphosphate (ATP). All the enzymatic reactions and synthetic processes catalysed by ATP require magnesium. Magnesium plays an important part in the maintenance of DNA structure and there is ample evidence to suggest that Mg^{2+} is intermediate complexing agent during cell duplication and the formation of RNA on a double-stranded DNA template (11). Magnesium and ATP are involved in the synthesis of nucleic acids. The sections of chromosomes in the nucleus are held together by magnesium and calcium, the changes in their concentration in the medium might affect the extent of chromosomal aberrations (11). Magnesium ions are essential for the physical stability of ribosomes responsible for protein synthesis, for the integrity of macromolecules necessary for RNA synthesis and for polypeptide formation (12). Magnesium (II) catalyses the reaction of ATP and creatine to produce ADP and phosphocreatine (13) but there seems to be no evidence for a direct interaction of the cation with the functional groups on the enzyme. However, ^{31}P NMR signals of enzyme-bound substrate complexes of creatine kinase established Mg^{2+} (14) and Mn^{2+} or Co^{2+} (15) as the cations which activate the enzyme. The atomic absorption and EPR spectroscopic studies of the metal-binding sites of bovine heart mitochondrial adenosine triphosphatase, revealed two sites specific for Mg^{2+} whereas one could be substituted with Mn^{2+}, Co^{2+} or Zn^{2+} (16). Bovine heart cytochrome c oxidase has been found to contain Mg^{2+}, Zn^{2+}, Cu^{2+}, Ca^{2+} and Fe^{2+}, each bound with high affinity as shown by resistance to removal by dialysis against various

media, and may have a catalytic and/or structural role in the enzyme (17).

Magnesium is quite abundant in human and animal body and like potassium occurs in high concentrations in the cells. Although there are many similarities in the metabolism of the two elements, magnesium is much harder to displace from the cell than potassium. Magnesium is so vital for life that its deficiency could result in a wide spectrum of manifestations particularly psychiatric and neuromuscular disturbances and delirium, caused by a large number of physiological disturbances such as malabsorption, inadequate food intake and renal depletion. The administration of magnesium parenterally or in the diet is necessary for the treatment of this often neglected syndrome (18).

METALS OF THE TRANSITION SERIES

Transition series metals are important in a wide range of biochemical functions in living tissues (19, 20):

1) Catalysis acting in the active centre of enzymes, co-enzymes or other important biological substances. Metal ions may be permanently attached to the active site e.g. Fe^{2+} in haemoglobin or metal coming and going as part of co-enzyme e.g. Co^{2+} in vitamin B_{12} co-enzyme;

2) Oxidation and reduction process such as in cellular respiration e.g. Fe^{2+} in cytochromes, catalases, peroxidases, phenol oxidases;

3) Biosynthesis and biodegradation of macromolecule viz. proteins, carbohydrates or lipids by formation and cleavage of bonds involving peptidases, dicarboxylases and phosphorylases e.g. metalloenzymes, Mn^{2+} or Zn^{2+} co-ordinating to nitrogen of amino and peptide groups and to carboxyl groups;

4) Stabilization of the conformation of macromolecules e.g. Zn^{2+} in insulin, Mn^{2+} in RNA and Ni^{2+} in RNA and DNA, Fe^{2+} in porphyrin complexes;

5) Storage and transfer of essential metals needed for other metabolic reactions e. g. ferritin;

6) Storage, transport or detoxification of toxic metals e.g. metallothionein or similar proteins.

Chromium is an essential trace metal, active in very small amounts. Its concentration may vary from a few ng/g in blood plasma to over 1 mg/g in some liver fractions. The concentration of chromium decreases in human tissues and increases in lungs with increasing age. Chromium in mainly two oxidation states (Cr^{3+} and Cr^{6+}) is relevant to the biological system. Although both forms of the metal are important for health, their effects on health are so fundamentally different that they require separate consideration. The co-ordination of trivalent chromium to bioligands is essential for its biological func-

tion and for its availability for the intestinal absorption. Under normal conditions, transition between trivalent and hexavalent chromium does not occur easily. However, hexavalent chromium might be reduced to the trivalent form at the physiological pH, especially in the presence of autoredox system e.g. by gastric juice with a significant decrease in toxicity. On the other hand, Cr^{3+} requires a high energy input for oxidation to Cr^{6+}. The reduction of Cr^{6+} to Cr^{3+} outside the cell or location other than the target site results in the formation of stable co-ordination compounds of Cr^{3+} with organic molecules whereby metal is rendered inactive towards functional biomolecules (21). Liver cell and endoplasmic reticulum are two organelle sites where reduction of Cr^{6+} to Cr^{3+} occurs. At normal physiological pH, simple inorganic chromium compounds are not soluble and the biological effects of the metal are expected from some complexed form(s). Thus, the chemical form influences the metabolism and biological availability of chromium (22, 23).

Hexavalent chromium has a potential to penetrate red cell membranes and is reduced to the trivalent form inside the cell which thereafter binds to haemoglobin resulting in tagging of the red cells. Trivalent chromium on the contrary, is unable to penetrate the red cell membranes but has shown a greater affinity than the hexavalent form for reaction with haemoglobin and binds easily to serum proteins (24). Trivalent chromium also binds to egg proteins and human plasma proteins strongly, while hexavalent chromium reacts, though weakly, with proteins only at low pH and the linkage further weakens as the physiological pH approaches.

Chromium influences several enzymatic reactions. In low amounts the metal activates oxygen consumption in succinic dehydrogenase, cytochrome system (25) and phosphoglucomutase (26) and the conversion of acetate to CO_2, cholesterol and fatty acids in liver (27). Chromium also stimulates the activity of renin, a protein-splitting enzyme (28). Chromium is regarded as an integral part of an important digestive enzyme, trypsin and plays an important role in the maintenance of its activity (29). Chromium has also been found to be part of nucleic acids and the metal is presumably co-ordinated to the components of nucleic acids. Its concentration ranges from 260 to 1000 μg/g of beef liver fraction consisting of 70% RNA and 30% protein. Even highly purified RNA fraction has been found to contain 50—140 μg/g of Cr (30). *Okada and co-workers* (31) have shown that Cr^{+3} specifically enhances the RNA synthesis and Cr^{+6} inhibits it in mouse liver; the synthesis of hepatic DNA and protein are not affected by Cr^{+3}. However, the thermal denaturation studies have shown binding of Cr^{3+} ion to bases on both DNA strands (32).

Inorganic chromium (Cr^{3+}) reportedly differs from that in certain organic complexes, called glucose-tolerance factor (GTF). The term GTF is used for many forms of biologically active chromium from

different sources. GTF is considered to be a heat resistant low molecular complex of one atom of trivalent chromium co-ordinated to two molecules of nicotinic acid, a cysteine, a glycine and possibly a glutamic acid molecule mainly occurring in the liver and kidneys. Its biological activity has been attributed to chromium and nicotinic acid moiety. Various studies have focussed on chromium-glucose-insulin interrelationship and the current hypothesis for the function of chromnium is that the metal acts as a potentiating agent for insulin and thereby helps to dispose off carbohydrates. Investigations on animals and humans have established the essential role of Cr^{3+} for the maintenance of normal glucose metabolism. The basic disturbance of chromium deficiency observed in malnourished children and in middle aged subjects, has been an impairment of the action of circulating insulin. Glucose intolerance is most common in humans and chromium deficiency might be one of the factors responsible for it. The protective role of chromium in the impaired glucose tolerance, diabetes and cardiovascular disease has attracted attention recently. The chromium supplementation has led to an improvement in glucose tolerance and a decrease in insulin levels. The latter is of great significance as elevated levels of insulin have been considered to be a risk factor in the etiology of cardiovascular disease (33). *Schroeder* (34) reported low chromium concentrations in the aorta of Americans compared to subjects in other countries with a low incidence of cardiovascular disease. An inverse relationship between coronary artery disease and chromium content in drinking water has been observed (35). Chromium has also been implicated in fatty acid and cholesterol synthesis (27) and might reduce serum cholesterol levels (36).

Manganese is an essential nutrient for growth. The metal occurs in trace concentrations in the cells of all living individuals and has established its role in many biochemical reactions and biological functions. Its functions in many cases cannot be taken over by other metals. Manganese exists mainly as Mn^{2+} and may co-ordinate with up to six ligands to give octahedral geometry (37). The divalent manganese (Mn^{2+}) ion has been well recognised as an activator of enzymes which includes hydrolases, decarboxylases, transferases and kinases (38). Manganese is exclusively required for the activities of some vital enzymes such as isocitrate and succinic dehydrogenases, cytochrome oxidase, pyruvate decarboxylase, peptidases, pyrolydase and malic enzyme (39, 40).

Pyruvate carboxylase is a mitochondrial manganese containing metallo-enzyme which catalyses the carboxylation of oxalacetate from pyruvate with manganese functioning in transcarboxylation step (41, 42). Pyruvate carboxylase is unique as it requires two metallic ions; Mg^{2+} for the carboxylation of the biotinyllysyl residue and Mn^{2+} for binding the keto compounds to the functional sites of the enzyme (43). Manganese also plays a role in the functions of enzymes involved in

carbon dioxide fixation viz. enzymatic carboxylation of phosphoenol pyruvate (37, 44), the activity of arginase (37, 45) and catalytic activity and stabilization of the quarternary structure of glutamine synthetase (37, 46). Interestingly, glutamine synthetase requires Mn^{2+} or Mg^{2+} but the affinity of the enzyme for Mn^{2+} is 400 times that for Mg^{2+}. Manganese acts as a co-factor for oxidative phosphorylation *in vitro*, particularly for coupling of phosphorylation to the oxidative reactions in mitochondria.

Manganese is also involved in oral glucose tolerance and in gluconeogenesis. The deficiency of the metal has been shown to result in impairment of oral glucose tolerance and abnormalities of pancreas which could be corrected by dietary supplementation of manganese (47). Thus, the importance of manganese for normal carbohydrate metabolism is evidenced by its presence in metalloenzyme-pyruvate carboxylase and its role in glucose utilization and the metal is indispensable for both the liver and pancreas.

Manganese stimulates synthesis of fatty acids and hepatic cholesterol (27) and acts as a co-factor in the conversion of mevalonic acid to sequalene (48). In the body system, most of Mn^{2+} becomes bound to α_2-macroglobulin in portal blood and is later removed from blood very efficiently by the liver. A very small portion of Mn^{2+} is oxidised to Mn^{3+} and binds to transferrin or transmanganin.

Iron is probably the most essential transition metal that occurs in highest concentrations in our systems generally bound to proteins. The adult human contains 3—4 g of total body Fe. The liver and spleen contain the highest iron concentration followed by the kidneys, heart, skeletal muscle, pancreas and brain. Iron has a versatile ability to form biocomplexes and depending upon the complexing bioligand attached to iron, the metal may be divalent e. g. myoglobin and haemoglobin which are involved as oxygen carriers; trivalent e.g. oxidases and catalases which are iron-porphyrin-protein complexes developed to protect the living cells from the noxious effect of hydrogen peroxide (formed from O_2 and H_2O) or resonate between the two states e. g. cytochromes which are responsible for oxidative phosphorylation generating adenosine triphosphate (ATP). However, iron may have a different electronic arrangement even within the same oxidation state e.g. Fe II in haemoglobin is high spin and in oxyhaemoglobin low spin. Other iron containing proteins are simple iron proteins e.g. ferrodoxins which occur in all photosynthesising cells, iron-sulphur proteins having either acid labile sulphide or cysteinyl sulphur e.g. acotinase, adrenidoxin, succinic and NADH dehydrogenases and xanthine oxidase; iron transporting proteins e.g. transferrin and lactoferrin; iron storage proteins occurring in almost all cells e.g. ferritin, haemosiderin (49). Ferritin also plays a role in the transport of iron across some cells and membranes. The plasma iron transport protein,

transferritin is the key intermediate in the internal redistribution of iron. Transferrin binds iron in the ferric state (Fe^{3+}) and the carbonate or bicarbonate anion is necessary for the formation of the complex.

There is a considerable movement of iron between plasma, bone marrow and red blood cells. The movement of iron between three pools is ruled by the red blood cells life span and 20 mg of Fe is released each day from dying red blood cells. This iron is returned to the bone marrow pool and is reincorporated into new red blood cells.

Xanthine oxidase, an iron flavoprotein enzyme responsible for the conversion of hypoxanthine and xanthine to uric acid depends on iron for its enzymic functions. Iron is an activator of tryptophan pyrrolase (50) and is an electron carrier in mitochondria. About dozen enzymes in the Kerbs cycle contain iron either as an active part of the molecule or require it as a co-factor.

Not much is known about the biological functions of cobalt. However, cobalt is considered important as being the central ion in cobalamines and cobalamide — Vitamin B_{12}, Co(III). Cobalamine is found in the liver and is essential for the synthesis of haemoglobin in humans. Cobalt (II) complexes are known to carry oxygen and simple complexes of cobalt (II) with ligands such as glycylglycine or histidine are capable of performing this function. Although the mechanism of cobalt action has not been completely worked out, the metal has been known to stimulate some enzyme systems such as haeme oxygenase, lactic dehydrogenase as well as arginase (45) and to inhibit the others such as citric acid cycle and hepatic drug metabolizing enzymes. Cobalt may compete with Mg^{2+} and Ca^{2+} ions which are required for enzymic activities (51). In general, Co(II) is known to be associated with low symmetry sites in enzymes. Cobalt may also share a common transport pathway through the intestinal mucosa with iron (52).

Nickel is associated with numerous biological functions within the human cell. It is most suited for a biochemical role in that it readily undergoes transition between several co-ordination structures and the available evidence indicates that the metal satisfies the criteria for essentiality of trace elements as micronutrients (3). Nickel binds to a variety of biomolecular structures such as nucleic acids, proteins and their constituent units viz. nucleotides, peptides and aminoacids. The sites of co-ordination include sulphydryl, amino, amido-N, phosphate and carboxyl groups.

Nickel (II) tightly binds to nucleic acid molecule as has been shown by the isolation of RNA with nickel content from different sources (30). Nickel binds to both the phosphates and the heterocyclic bases of DNA (53, 54) and RNA and stabilizes their conformation (55). The binding of nickel (II) to DNA could play a role in the inhibition of RNA polymerase. The binding of nickel (II) to adenosine triphosphate (ATP), an important cellular constituent involved in energy transfer

and many enzymic reactions, may be considered significant (56, 57). Nickel has been shown to bind to the pyrophosphate group and the pyrimidine bases of thiamine pyrophosphate which acts as a co-enzyme in many enzymic reactions (58). Nickel ions like other metal ions can catalyse transamination involving the transfer of an amino group from aminoacid to a keto acid in the presence of vitamin B_6. The catalysis proceeds through the formation of a nickel complex of Schiff base between the keto acid and pyridoxamine, followed by a shift of a double bond which converts the initially produced Schiff base into the Schiff base of pyridoxal and the aminoacid corresponding to the keto acid (58).

Nickel plays an important role in the metabolism or structure of membranes. Nickel may substitute calcium in certain steps of excitation-contraction coupling of isolated skeletal muscles (59), excitation process of the isolated nerve cells (60) and in the binding to membrane ligands such as the phosphate group of phospholipid in the process of nerve transmission and muscle contraction. Nickel may activate numerous enzymes *in vitro* including arginase, tyrosinase, deoxyribonuclease, acetyl co-enzyme A synthetase and phosphoglucomutase (45, 61, 62). Indirect but suggestive evidence that nickel plays a role in the pigmentation and the possibility that the metal plays a role in lactation at the pituitary level have been advanced. Nickel may be important in the regulation of prolactin. The yellow pigments and plasma cholesterol due to nickel deficiency may be related to its effects on hormones (63). Serum albumin is the main carrier protein for nickel in human and other mammalian sera (8). A second macromolecular carrier in human sera is a nickel rich metalloprotein, the nickeloplasmin (64). Nickeloplasmin is believed to be an α-macroglobulin possessing trypsin-protein esterase activity characteristic of serum α-macroglobulins (65).

Copper is essential for the synthesis of cytochrome oxidase and has established itself as biochemically significant catalyst (66). Copper or iron in catalytic amounts mediates the reduction of cytochrome c by thioglycolic acid (67). *Starcher* (68) first identified the copper binding protein — the thionein. A soluble, heat-stable, copper rich protein with a molecular weight $\sim$ 12000, a SH : metal ratio of $\sim$ 3 and a typical UV maxima at 272 nm, characteristics common to Cu-thioneins, has been isolated from the tissues of mussels exposed to copper (69). The hepatic Cu-thionein may participate in the detoxification process as well as in the intracellular transport of the metal. Within hepatic cells, copper initially bound to a copper binding protein eventually appears in ceruloplasmin, copper dependent enzymes and bile component (70). In metalloproteins containing more than one metal ion, copper tends to appear in even numbers e.g. cerebrocuprein has two copper and ceruloplasmin has eight copper atoms. The ceruloplasmin is a transport protein and utilizes its copper in the biosynthesis of cytochrome

oxidase. After the isolation of haemocuprein, several copper containing enzymes have been isolated and characterised (71). Copper enzymes are unique in catalysing the reduction of molecular oxygen to water. Copper, in oxidation states I and II and cuproproteins can also carry oxygen e.g. haemocyanin. Copper besides iron is the best catalyst for the oxidation-reduction processes. Superoxide dismutase, lysyl oxidase, lactate oxidase, monoamine oxidase and dopamine β-hydroxylase have been identified as copper enzymes which catalyse physiologically important reactions such as the metabolism of catecholamines, metabolic activity of connective tissues and scavenging of superoxide radical.

Copper also plays a significant role in the cross linking and maturation process (72). Copper in new born liver is chiefly accounted for by mitochondrocuprein, a protein extra-ordinarily high in copper localized in the mitochondrial fraction and specific to the neonatal period. The role of copper in the connective tissue is linked to the enzyme lysyl oxidase. The role of copper in maintaining normal neurological function has also been described. Dopamine β-monooxygenase is the copper metalloenzyme in the catecholamine biosynthetic pathway (73).

Zinc, after absorption, is deposited in soft tissues and in the bone. Although bone accounts for an appreciable percentage of the total body zinc, this pool is hardly available. A considerable portion of body zinc not associated with bone is found in the liver and intestine. This fraction of zinc represents a metabolically active compartment. Zinc in plasma is mostly bound to albumin but other proteins such as α_2-macroglobulin, transferin, ceruloplasmin and haptoglobin also bind significant amounts of this metal (8, 74). Human serum high density lipoprotein (HDL) has been found to contain Zn^{2+} and Ca^{2+} which contribute to the interaction between lipids and apolipoproteins in HDL particles (75). Besides the protein bound fraction, a smaller amount of zinc in plasma exists as an ultrafilterable fraction mostly bound to aminoacids. The most important function of zinc in human and animal metabolism is its association with various enzymic reactions (76, 77). Zinc and a few other divalent metals such as copper, cobalt and nickel have been shown to inhibit the autophosphorylation reaction responsible for the conversion of insulin receptor from human placenta to an active tyrosyl-protein kinase which is significant as Zn^{2+} is accumulated in and secreted from pancreatic islet cells together with insulin (78). Although zinc exhibits one oxidation state *in vivo*, it is most essential to several metalloenzymes. Over 70 metalloenzymes are reported to require zinc for their functions (79). Zinc is present in several dehydrogenases, aldolases, peptidases and phosphatases. Thymidinekinase is a zinc dependent enzyme and it is very sensitive to zinc deficiency (80). The chemical stability may be an essential aspect of the utilization of zinc in diverse biological processes such as hydrolysis, transfer and addition to double bond and even oxireduction. The

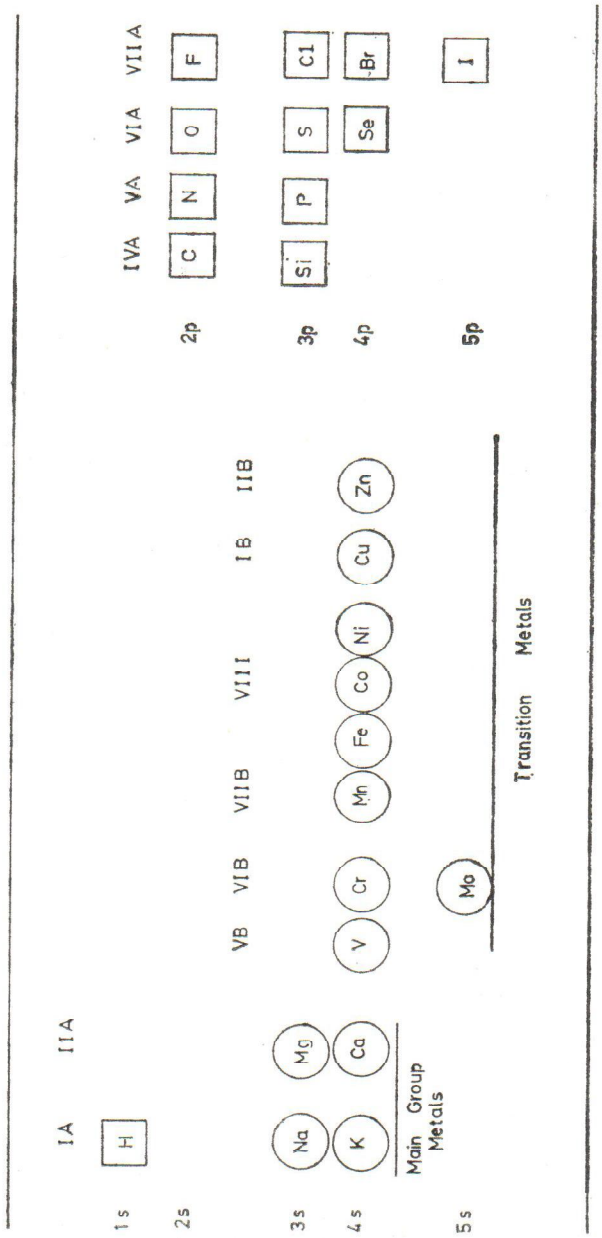
role of zinc in redox enzymes such as alcohol dehydrogenase is not to donate or accept electrons but rather to serve as a Lewis acid. It is this capacity to serve as a super acid that underlines the functions of zinc in many metalloenzymes (81). Zinc is also an essential constituent of both DNA and RNA polymerases. Zinc plays a role in the maintenance of polysome profile in the liver. A low molecular weight metal binding protein, metallothionein (MT) has been shown to possess high sulphydryl and zinc contents. Liver MT contains predominantly zinc and is believed to serve as a storage protein of zinc (82). It appears that the synthesis of metallothionein provides the intestinal cell with an additional pool of binding sites with which to alter the net flux of zinc ions.

Vanadium is an important co-factor in controlling one or more enzymic or catalytic reactions. Vanadium functions as an oxidation-reduction catalyst in the biological system (83). The presence of vanadium in tissues might inhibit phosphoryl-transfer enzymes *in vivo*. The *in vivo* studies have shown vanadium in valence state 5^+ to be a potent inhibitor of sodium and potassium adenosine triphosphatase and other phosphoryl-transfer enzymes which leads to the hypothesis that vanadium should function as a regulator of sodium and potassium ATPase and thus the sodium pump (84). The regulatory function for vanadium is evidenced by an *in vivo* mechanism, whereby vanadium which exists in the tissue in the relatively inactive 4^+ oxidation state complexed to protein or small molecules, would be converted to the 5^+ state (85). There is a considerable evidence that vanadium is involved in the metabolism of lipids (86) and pharmacological levels of vanadium may affect tissue cholesterol levels. The altered cholesterol levels have been correlated with the vanadium inhibition of the microsomal enzyme system (Squalene synthetase) and with the vanadium stimulation of aceto-acetyl co-enzyme A deacylase in hepatic mitochondria (87). Vanadium also has a catalytic or enzymic function in bone metabolism or formation.

Molybdenum is the heaviest essential metal. It has most important role in the xanthine and purine metabolism (19). The biochemical functions of molybdenum in living beings are related to the formation and activities of three molybdenum containing enzymes (88). The first two of these are involved in the electron transport chain in the cells. Molybdenum participates in the reaction of xanthine oxidase with cytochrome C and facilitates the reduction of cytochrome C by aldehyde oxidase (89). Aldehyde oxidase like xanthine oxidase when complexed with molybdenum, possesses a marked ability of facilitating the interaction with cytochrome C. Molybdenum is present at the substrate binding sites in both these enzymes (90). Molybdenum also participates in redox reactions (V VI) and even the III and IV oxidation states are suspected to be involved (91). This element is also required for

Table 1

Part of the Periodic table showing elements essential for the life



growth, cellular oxidation, purine metabolism and is possibly involved in iron metabolism.

This review emphasizes the requirement and the extent of participation of certain metals in our body functions and dynamics. It is rather impossible to imagine life without essential elements. A considerable evidence has been offered to justify the inclusion of all the metals discussed, in the category of essential elements. Only useful aspects of these metals which are vital for the biological functions have been included in the present review. However, high doses of essential metals may cause acute intoxication. For example, ingestion of soluble salts of iron, zinc or copper in a dose of several hundred milligrams induce nausea, vomiting, abdominal pain or diarrhoea. The participation and transport of metals in the biological systems at the intracellular level are essentially a function of bioligand composition and transport which varies with species, organ, cell and organelle compartment. The bioligand may be divided into low or high molecular weight compounds. The most important low molecular weight compounds include glutathione, cysteine, co-enzyme A, dihydrolipoic acid, histidine, other aminoacids, citrate, pyrophosphate and nucleoside phosphates while the high molecular weight ligands may be metallothionein, transferrin, ferritin, ceruloplasmin, serum albumin, metal binding enzymes and nucleic acids. Thus the role of *in vivo* co-ordination chemistry must be recognised. It is hoped that the continuing efforts to investigate the metabolism of metals, would not only reveal many hitherto undiscovered biological roles of essential metals but may also help in extending the list of essential metals.

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Sažetak

ESENCIJALNI METALI U BIOKEMIJI

Opisane su temeljne biokemijske funkcije esencijalnih metala. Klasificirani su u dvije osnovne skupine: mobilni u ionizirajućem stanju i tranzicijski metali, koji su kovalentno vezani za bioligande. Od mobilnih esencijalnih metala posebno su istaknuti kalcij i magnezij. Opisana je uloga magnezija u procesu oksidativne fosforilacije te u sintezi nukleinskih kiselina i proteina. Manjak magnezija može dovesti do neuromuskularnih poremećenja. U drugoj skupini opisana je uloga kroma i to posebno trovaljanog i šesterovaljanog. Krom utiče na mnoge enzimske reakcije a stimulira i aktivnost renina. Krom igra značajnu ulogu u metabolizmu glukoze pod utjecajem inzulina, tako da se njegov manjak povezuje s poremećajem djelovanja inzulina. Mangan je esencijalan za rast i njegov se učinak ne može zamijeniti nekim drugim elementom. Željezo se smatra najvažnijim esencijalnim metalom s raznolikim ulogama u biokompleksima. Kobalt se ističe svojom značajnom ulogom u građi vitamina B_{12}. Nikal se veže za različite biološke strukture kao što su bjelančevine, nukleinske kiseline ili amino kiseline. Uloga mu se posebno ističe u transaminaciji te u strukturi i funkciji membrana. Bakar uz željezo ima značajnu ulogu u kataliziranju različitih reakcija posebice u metaboličkoj aktivnosti vezivnog tkiva. I cink je prisutan u mnogim enzimima, posebice u dehidrogenazama, aldolazama itd. I vanadij i molibden igraju značajnu ulogu u različitim katalitičkim reakcijama.

Premda su esencijalni metali u malenim dozama neophodni za normalno funkcioniranje organizma, njihova prevelika količina može dovesti do toksičnih učinaka.

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