Metal Transport across Human Cell Membranes

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Abstract

The field of ‘inorganic biochemistry’ is rapidly changing due to metal ions properties which are rendered indispensable in cellular biochemistry. At least, twenty six of the hundred eighteen periodic table elements are now known to be involved in the biochemistry of the human body. Their various physical properties are utilized in a subtle and sometimes unexpected ways to serve biochemical purpose. The essential trace elements or inorganic micronutrients invariably have a catalytic function, and are found in the metabolic pathways controlling other substrates assimilation and utilization in the synthesis of new cells and in the use of cell energy. Many studies have exposed that the imbalance of zinc, iron, and copper which are cofactors of many enzymes, can affect various cancers and diseases like Alzheimer’s, Parkinson’s and hypertension. The pathogenesis of essential hypertension is associated with increased exchangers activity of Na^+/Li^+, Na^+/H^+ and Na^+/K^+ ATPase. Therefore, it is crucial to develop an inclusive understanding how regulating metal levels in human body is of importance to eliminate any significant effects of various toxic metals on human health. The syndromes of pneumoconiosis, neuropathies and hepatorenal degeneration develop slowly over time and it may be difficult to diagnose chronic exposure to metal dusts. Therefore, this review is restricted to the normal biological activities of metals, though the gross physiological effects of metal deficiency or toxicity will not be ignored.

Keywords: Biochemistry of metal absorption in human body; bioinorganic chemistry; bioavailability; metal toxicity; human health; contamination; nanoparticles; micronutrients; homeostasis; metallochaperones; bioavailability.

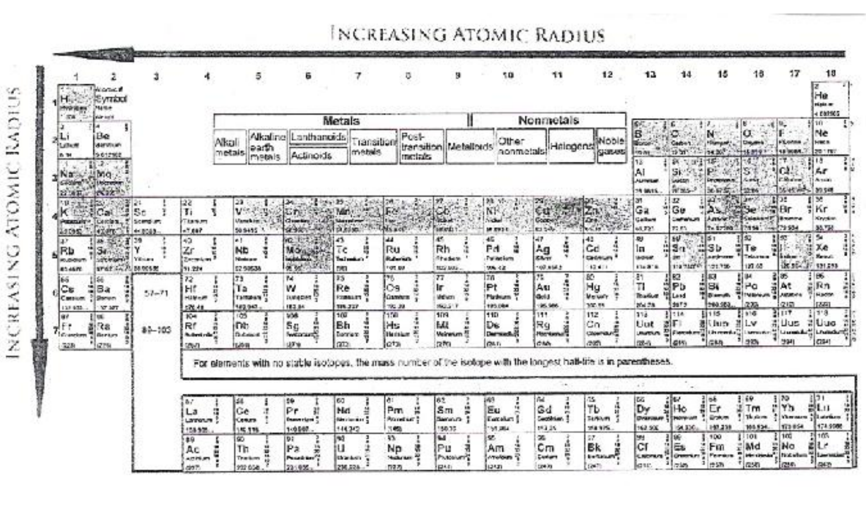
Introduction

The human body contains chemical compounds such as water, proteins, carbohydrates, lipids, nucleic acids, apatite in bones, dissolved inorganic ions , gases, free radicals and many other small molecules such as amino acids, fatty acids, nucleobases, nucleosides, nucleotides, vitamins and cofactors (Nelson and Cox, 2008). These chemical compounds from the periodic table elements (Table 1) consist of dietary 'bulk' elements such as oxygen, carbon, hydrogen, nitrogen, calcium and phosphorus that make up a total of ~98.7% of human body mass (Zumdahl and Zumdahl,2006) . Some of these elements have no clearly-identified biochemical function in human cells as yet, but they demonstrate deprivation effects on human body (Shils et al., 1999; Chang, 2007). Also, all of these chemical compounds and elements occur in various forms and combinations in plants and animals that humans feed on (Bertini et al, 2007; McDonald et al., 2009). The chemical elements and compounds are ingested, digested, absorbed, and circulated through the bloodstream (Da Poian et al., 2010).The list will undoubtedly grow as experimental techniques improve. However, the ultimate aim of this review is to express metal activities in human body.

Table 1: Periodic table for dietary minerals.

The elements common within human cells are highlighted.

Adopted from: Casey, C.E. and Robinson, M.F. (1983) Some Aspects of Trace Element Research, in Metal Ions in Biological Systems, Sigel, H. (ed.), pp.1-26. New York, NY: Marcel Dekker; Gibson, R.S. (1990) Principles of Nutritional Assessment. Oxford: Oxford University Press ; Shils, M.E., Shike, M., Ross, A.C., Caballero, B. and Cousins, R.J. (1999) Modern Nutrition in Health and Disease, 9th edn. Baltimore, MD: Lippincott Williams & Wilkins.



Metal ions have a very unique chemical properties (Feausto da Silva and Williams,2001; Bertini et al., 2006) that allows them to play diverse roles in human cellular biochemistry (Halliwell and Gutteridge, 1999; Willett, 2002). These properties have rendered 23 elements (Fraga, 2005) of known physiological activities indispensable for *Homo sapiens* of genome nucleotide pairs $3.1x10^9$ and the number of genes $2.9\ x10^4$ (Nelson and Cox, 2008,p.35).

Due to the earth formed around $4.54x10^9$ years ago (Encrenaz ,2004) ; the essentiality of metal ions in a 70kg human body (major >200mg/day< minor) is unquestionable relative to the abundance of inorganic minerals in Earth's crust where oceans cover 71% of Earth's surface and 95% of the planet's water (Gleick, 1993; Chang 2007); and the bioavailable ionic elements that are needed for life are prevalence in the Earth's crust (Table 2) roles in living cells (Frieden,1974; Milne, 1999; Craig et al., 2001). Some metals have unique chemical properties which give them unique roles in the human body. For example, calcium and magnesium particularly are with highly distinctive physiological roles that meet the specificity requirements of the human body. Hence, calcium is required for clotting of blood, controlling functions of nerves and muscles, and for the formation of strong bones and teeth (Seifter, et al., 2005).

Table 2: The elements of life and their abundances in Earth's crust.

The earth's crust includes the terrestrial waters and the atmosphere; the numbers are estimates as they vary in subject to their source and method of calculation.

ΔH^{θ}_{a} denotes the enthalpy of atomization, i.e. the standard enthalpy of the formation of gaseous monoatomic element at $298^{o}K$ and 101325 Nm^{-2} (1 atm) pressure.

Adopted from: Mason, B. (1958) Principles of Geochemistry, 2^{nd} edn, p.44. New York, NY: John Wiley & Sons., Inc.;Shils, M.E., Shike, M., Ross, A.C., Caballero, B. and Cousins,R.J. (1999) Modern Nutrition in Health and Disease, 9th edn. Baltimore,MD: Lippincott Williams & Wilkins; Frausto da Silva, J.J.R. and Williams, R.J.P. (2001) The Biological Chemistry of the Elements: the Inorganic Chemistry of Life. New York, NY: Oxford University Press; Chang, R. (2007) Chemistry, 9th edn, p.52. Ney York, NY: McGraw-Hill; Bertini, I., Gray, H.B.,Stiefel, E.I. and Valentine, J.S. (2007) Biological Inorganic Chemistry. Sausalito, CA: University Science Books.

No.	Element	Earth's crust % by volume	Human body % by mass	ΔH^{θ}_{a}/ kJ.mol^{-1}
	Major Elements			
1	Oxygen (O^{-2})	46.600	65.000	248
2	Carbon	0.030	18.000	715 (graphite)
3	Hydrogen (H^{+})	0.140	10.000	218
4	Nitrogen (N^{-3})	0.005	3.000	473
5	Calcium (Ca^{2+})	3.630	1.500	193
6	Phosphorus (P^{3-})	0.120	1.200	315 (white)
7	Potassium (K^{+})	2.590	0.250	90
8	Sulfur (S^{2-})	0.050	0.250	223 (β)
9	Chlorine (Cl^{-})	0.050	0.150	121
10	Sodium (Na^{+})	2.830	0.150	109
11	Magnesium (Mg^{2+})	2.090	0.050	150
	Minor Elements			

12	Iron (Fe^{+3}, Fe^{+2})	5.000	0.006	418
13	Cobalt (Co^{+2}, Co^{+3})	0.003	$2.1x10^{-6}$	427
14	Copper (Cu^{+2}, Cu^{+})	0.010	$1x10^{-4}$	339
15	Zinc (Zn^{2+})	0.007	0.003	130
16	Iodine (I^{-})	$4.9\ x10^{-5}$	$1.6x10^{-5}$	107
17	Selenium (Se^{2-})	$5.0\ x10^{-6}$	$1.9x10^{-5}$	202
18	Fluorine (F^{-})	0.054	$3.7x10^{-3}$	79.1
19	Nickel (Ni^{2+}, Ni^{3+})	0.008	$1.4x10^{-5}$	431
20	Chromium (Cr^{3+}, Cr^{2+})	0.020	$2.4x10^{-6}$	398
21	Manganese (Mn^{2+}, Mn^{4+})	0.100	$1.7x10^{-5}$	279
22	Strontium (Sr^{2+})	0.045	$4.6x10^{-4}$	164
23	Vanadium (V^{3+}, V^{5+})	0.011	$2.6x10^{-5}$	515
24	Arsenic (As^{3-})	$2.1x10^{-4}$	$2.6x10^{-5}$	290
25	Silicone (Si)	27.720	$2.0x10^{-3}$	439
26	Tin (Sn^{4+}, Sn^{2+})	$2.2x10^{-4}$	$2.4x10^{-5}$	301
27	Boron (B)	$8.7x10^{-4}$	$6.9x10^{-5}$	590
28	Molybdenum (Mo^{6+})	$1.1x10^{-4}$	$1.3x10^{-5}$	651

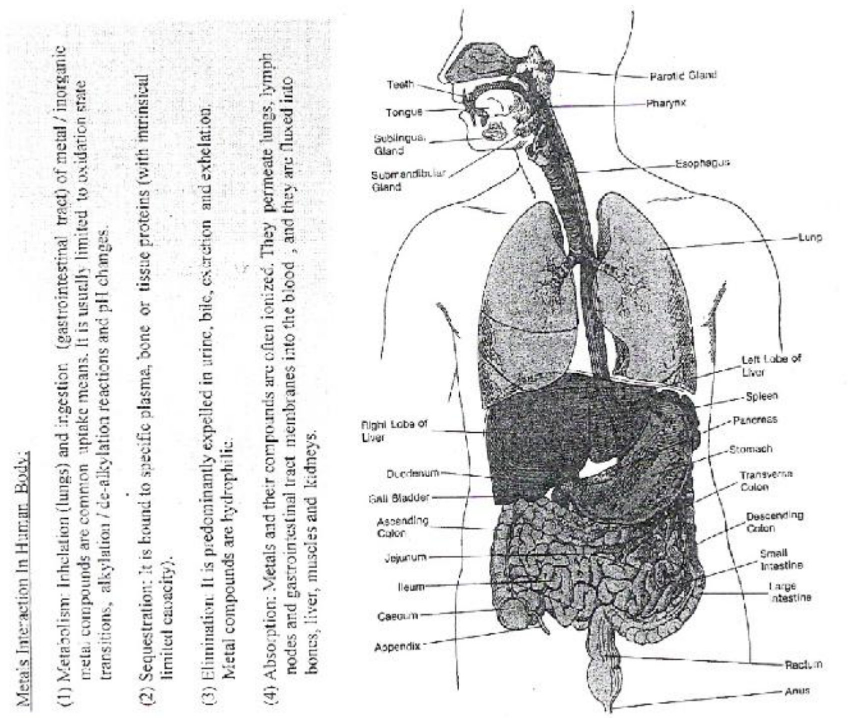
Whereas magnesium has key roles as a cofactor of many enzymes such as [EC2], [EC3],[EC5] and [EC6] linked to physiological processes and ATP dependant metabolic reactions (Bugg, 1997). Also, biochemical binding sites, especially high affinity ones, are tailored to suit particular metal and no other. Metalloproteins with redox functions are especially demanding in metal specificity, but often there seems to be little reason why a different metal bound to a different protein might not serve as an identical biochemical purpose. Copper proteins can mimic iron proteins in almost all their varied functions at a chemical level, yet oxidative phosphorylation is almost totally dependent on iron (Oexle et al., 1999; Beard, 2001; Feiters, 2001; Xie and Collins, 2013). The explanation may be historic in part, involving not only the suitability and availability of a metal, but the evolution of a protein to bind it and interact with other metabolic molecules as required (Fig.1), and also the transport processes to deliver it to its binding site (Wessels and Hopson, 1988; Siram et al., 2005).

Fig.1. Human digestive system.

The major anatomical organs of the human gastrointestinal are used basically for motility, secretion, digestion and absorption.

Adopted from: Wessels, N.K. and Hopson, J.L. (1988) Biology, p.821.New York, NY:

Random House. Inc. ; Patil, Y. P., Pawar, S.H., Jadhav,S. and Kadu, J.S. (2013) “Biochemistry of metal absorption in human body: reference to check impact of nano particles on human being”, Int. J. Sci. Res. Pub, vol.3 (4), p.2251



Human body requires major and minor elements which are generally found in fresh vegetables, fruits, fish, meat, dairy products, eggs, cereals, nuts, legumes etc. to serve several purposes (Kennedy and Meyers, 2005). The deficiency of such elements in human body may occur as a result of inadequate dietary intake or blood loss which creates different types of functional or structural abnormal health problems and diseases (Calabrese et al., 1985; Jackson, 1999; Shilset al., 1999; Fraga, 2005). The entry of these elements and other 'nanoparticles' to human body take place through the digestive and respiratory systems and their constant concentrations are maintained by homeostasis (Nelson, 19999; Bleackley and Macgillivray, 2011).

It had been suggested that a site of hydrothermal system would be more likely used in forming first complex organic substances (Miller and Urey, 1959; Waldrope,1990 ; De

Duve, 1996; Lazcano and Bada, 2004). The biological importance of such substances chemical elements tends to be parallel to oceanic abundance (Frieden, 1974; Robertson, 1996; Frausto da Silva and Williams, 2001), though the parallelism in higher forms of life was subjected to natural selection process to enable the elements performing vital function (Darwin, 1859; Carrol, 2006). This aspect of evolutionary events might be of relevance in understanding both the essentiality and toxicity of metals for life (Friedman, 1985; Nielsen, 1997).

Many biochemical roles for both minerals and organic compounds evolved when such molecules were abundant. If they became less available, cells would develop appropriate mechanisms to accumulate them, by concentration or biosynthesis (Chiti and Dobson, 2006). Past environmental abundance is a further possible determinant of present-day specificities for metal ions, using information from chemical, fossil and geological studies to throw more light on this evolutionary aspect of metal biochemistry in human body (Pereto, 2005; Bertini et al., 2007).

Living humans have many different requirements for metals. Metals main function is to maintain osmotic and electrical charge balance that serves as transmembrane electrical potential (Hajjawi, 2012a; 2013a), hence providing a general cationic environment (Monachese et al., 2012), and mediating electron transfer of metaloenzymes. Therefore, the major metals involved in these roles are shown in Table 3.The requirement for [K^+] and [Mg^{2+}] serve as counter-ions for the various macro-molecules and stabilize their structure. Although Mg^{2+} is accumulated in lesser quantity than K^+, it is equally vital in stabilizing or activating intracellular phosphates (Swaminathan, 2003). These include nucleic acids as well as small molecules and phospholipids in the cell membrane.

(Jehnen-Dechent and Ketteler, 2012). $[K^+]$ is the principal cation mediating osmotic balance with the external medium, and it is accumulated in concert with the efflux of $[Na^+]$. This Na^+/ K^+ separation has allowed the evolution of the reversible trans-membrane electrical potential essential for action across plasma membranes. Thus, the membrane potential is a function of the concentration of permeable ions on both sides of the membrane and Nernst-Planck equation **(**Hodgkin et al., 1949; Schmuck, 2012; Hajjawi, 2013a and 2013b).

Table 3: Major ions concentration in human red blood cells.

$[C]_i$: intracellular concentration, whereas $[C]_o$: extracellular concentration.

Adapted from: Hajjawi, O.S. (2012a) "ATP/ATPase and flux activities in human red blood cells", Eur. J. Sci. Res., vol. 93 (3), p.425;

Ellory, J.C. and Lew, V.L. (1977) Membrane Transport in Red Cells.

London: Academic Press Inc,(London) Ltd; . Stearcy, R.L. (1969) Diagnostic

Biochemistry,p.133,p.374,p.429,p.470.New York, NY: McGraw-Hill Book Company.

	Na^+	K^+	Mg^{2+}	Ca^{2+}
Radii (pm) 1Å=100pm	102	138	72	100
[Cation] of erythrocyte:				
$[C]_i$ (mM)	16	140	$5x10^{-1}$	$1x10^{-4}$
$[C]_o$ (mM)	140	4	2	2
$\ln[C]_i / [C]_o$	-2.169	+3.555	-1.386	-9.903
$V_m = RT/zF.\ \underline{\ln}[C]_I/[C]_o$ (mV) at 37° C	-57.9	+94.9	-18.5	-132.2

[Cation] of various body fluids (mg/100ml):				
Amniotic fluid	127	4.9	1.8	7.2
Aqueous humor	179			
Bile: Liver Gallbladder	134-156	2.6-12.0	1.5	4.0-9.0 10.0-14.0
Cerebrospinal fluid	129.2-153.2	2.2-2.9	2.40	3.9-5.1
Duodenal secretion				12.4
Formed stools	7-96			
Gastric juice: Total Fundus Pyloric	31-90 35 160		1.8-7.7	4.0-9.6
Ileal secretion	112-142	5.9-29.3	15.1-22.9	5.0-12.8
Intestinal juice	72-128			
Jejunal secretion: Upper Lower				5.2-11.6 5.4-12.8
Lymph, thoracic duct	118-132	3.9-5.6		8.6-11.8
Milk, immature: Colestrum Transitional Milk, mature	11-60 8-24 3-19	 9-18	 1.5-4.7	 7-61
Pancreatic juice	141.1	2.6-7.4	0.3	4.4-6.4
Peritoneal fluid	127-155	2.0-5.6	0.5	4.09.8

Pleural fluid	136-148	2.5-6.6	0.72-2.41	5.6-10.8
Prostatic fluid	149-158	29-61	1.0	114-130
Saliva	33.1	14-38	0.16-1.06	5.2-9.7
Semen	105-152	17-27	12.0	14-62
Serum ,adult	136.6-141.8	3.4-4.8	1.95	8.4-11.2
Sweat	58.4	21-126		1-8
Synovial fluid	132.8-139.4	3.5-4.5		8.3-10.7
Tears	108.4-175.6	7.7-22.1		
Transudates	122-156	2.8-6.0		5.2-9.8
Urine (mg/kg body wt/day)	40-156	16-56		0.6-8.3
Vitreous humor	118-154	3.3-12.0		5.6-10.4
Whole blood	91.8-96.2		3.5	9.7

Furthermore, it is assumed that many biochemical roles for both minerals and organic compounds would be evolving as such molecules were abundant; if they become less available, cells develop appropriate mechanisms to accumulate them by means of biosynthesis or concentration (Lippard and Berg, 1994; Frausto da Silva and Williams,2001; Pallack and Chin, 2008; Moreno et al.,2012). Past environmental abundance is, therefore, a further possible determinant of present-day specifications for metal ions physiology using chemical, fossil and geological studies (Smith et al., 1999; Sharov, 2006).

Many enzymes require metal ions (Na^+, K^+, Mg^{2+}, Ca^+, Zn^{2+}, Mn^{2+}, Cu^{2+} , Fe^{2+} and Co^{2+}) that can stabilize macromolecular structure, participate in cross-linking , redox and non-redox catalytic roles, metal metabolism, affect the binding of small molecules and catalyze their reaction (Williams, 1970; Frausto da Silva and Williams ,2001). The remarkable substrate specificity of enzymes had led to a rather rigid structure, the 'lock' which could only be fitted by the corresponding 'key'; however, the substrate (Fischer, 1894) and an enzyme's function may sometimes depend on its flexibility (Koshland, 1958).Many enzymes could be reversibly unfolded and smaller local active structural conformational changes could be induced by smaller molecules not necessarily in any way related to the substrate. In Metal, ions may induce conformational changes in enzymes. They may enhance or inhibit enzyme activity. The empirical distinction between metalloenzymes (which have functional and tightly bound metal) and metal-activated enzymes (which have structural and loosely bound added metal for activity) is in the metal ion isolation, whether $pK_{Dissociation}$ for metal binding is greater or less than 7-8 and it is of quantitative nature (Jakson et al., 2001; Thompson et al., 2011). In the latter enzymes, the affinity to metal is low (Banci, 2013). Enzymes are impressive for their incredible substrate specificity, reaction selectivity, stereo specificity, lowering the activation energy and tremendous efficiency which is typically 1 to 10 million times or more as efficient as inorganic catalysts (Sheldon, 2000). As a result of very rapid enzyme cycle, a tiny amount of enzyme is required; thus this has made the isolation and study of enzymes quite difficult (Hajjawi, 2011; 2012b). Hence, enzymes classification system is based on the type of reaction an enzyme catalyzes (Cotton and Wilkinson, 1988; Nelson and Cox, 2008).There are six principle categories:

[EC1] Oxireductases which are involved in electron transfer, incorporating Fe^{2+} and Cu^{2+}. Example: lactodehydrogenase [EC 1.1.1.27]. [EC2] Transferases which transfer a chemical group from one substrate to another, incorporating Mg^{2+} and Mn^{2+}. Example: ATP: D-Hexose 6- transferase [EC 2.7.1.1]. [EC3] Hydrolases which cleave substrates by utilizing H_2O molecules, incorporating Zn^{2+}, Ca^{2+} and Mg^{2+}. Example: β-Galactosidase [EC 3.2.1.23]. [EC4] Lyases which form double bonds by adding or removing a chemical group, incorporating Mg^{2+} and Zn^{2+}. Example: L-Malate hydro-lyase [EC 4.2.1.2].
[EC5] Isomerases which transfer a chemical group within a molecule to form an isomer, incorporating Mg^{2+} and Mn^{2+}. Example: D-Glyceraldehyde-3-phosphate ketoisomerase [EC 5.3.1.1]. [EC6] Ligases which couple the formation of various chemical bonds (synthases), incorporating Mg^{2+} and Mn^{2+}. Example: Glutamine synthase [EC 1.4.1.13].

Various theories have been put forward to explain the very high efficiency of enzyme-catalyzed as compared with non-enzymic reactions (London et al., 1962; Fersht, 1998; Menger, 2005; Fogel, 2011), though we shall mention here two hypotheses that relate to metals in catalytic roles. Gilbert Newton Lewis (1875-1946) suggested that covalent bonds frequently involve the pairing of electrons, and in doing so, atoms often reach the electronic configuration of the inert gases. On that basis, metal enzymes contain a ‘super-acid’ in neutral solution, i.e. the bound metal presents a centre of positive charge, available for Lewis-acid catalysis, in pH ranges where comparable proton catalysis is ineffective, and where the free metal ion might be precipitated as an hydroxide. Such a metal can interact with substrate molecules by polarizing bonds, neutralizing negative charge, spacially disposing ligands, and stabilizing transition states or intermediates

(Andreini et al., 2008). The second hypothesis stems from spectroscopic of transition metals as they may be bound in co-ordination geometrics of different natural ligands arrangement with small molecules in solution, thereby prompting strained state stereo specificity of enzyme active site and catalytic efficiency (Williams, 1970; McCall et al., 2000). In fact, strained states are associated with redox enzymes and carriers, but this is not a rule for non-redox enzymes. For example, phosphoglucomutase [EC 5.4.2.2] that transfers α-D- glucose monomer from the 1' to the 6' position requires metals in unstrained octahedral co-ordination for activation (Sutherland, 1949; Dixon et al., 1976; Dai et al., 1992; Nelson and Cox, 2008). Table 3 shows that Ca^{2+} is a larger divalent cation than Mg^{2+} and it is the metal that crosslinks macromolecules or induces large conformational changes in them. With small legands, Ca^{2+} and K^{+} are usually octa-co-ordinate, while Mg^{2+} and Na^{+} are hexa-co-ordinate; and enzymes active sites are inactivated by a change of metal radius of 20 pm or less with more tolerance when metal has a purely structural role (Skou, 1957; Howarth et al., 2012), though minor metals normally cannot substitute for Mg^{2+} or Ca^{2+} emphasizing that other factors are also involved in specificity criteria (Jomova and Valko, 2011; Singh et al., 2011). The relative kinetic inertness of Ni^{2+} to ligand substitution probably explains why it is not such a good substitute for Mg^{2+} as it is Mn^{2+}, even though it is closer in size (Williams, 1982). On the other hand, Co^{2+} has been used as a spectroscopic probe in Zn^{2+} enzymes like carbonic-anhydrase β [EC 4.2.1.1] and carboxyprptidase A [EC 3.4.17.1] , and it provides an effective substitution as they are close in size, ligand co-ordination geometry and comparable activity (Anderson and Vallee, 1975; Reilly, 2004; Bennett, 2010).

Metal metabolism

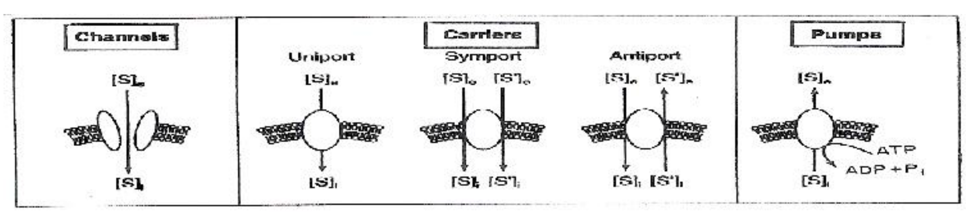
Uptake, transport, buffering, storage and excretion of metal ion must ensure that physiologically necessary metals are made available to act where they are needed, though they are not in excess. These activities are regulated by sensors that govern the carriers, storage molecules and detoxification, such that the deleterious metals are rendered harmless (Bowen, 1966; Nielsen, ,1997; Luk et al., 2003; Finney. and O'Halloran, 2003; Da Poian et al., 2010). Free metal ions are hydrophilic and they cannot readily diffuse across the lipid bilayer of the cell membrane (Campbell and Farell, 2009). They require to be a fat soluble compound or to have carrier molecules (Fig. 2). Many metals are taken up into the cell by mechanisms of relatively low metal affinity and specificity (Stonell and Savigni, 1996; Zhang et al., 2001). Therefore, the transportation of metals from the gut lumen to the blood stream involves traversing mucosal epithelial cells and capillary endothelial cells (Conrad et al., 1967; Barett et al., 2012). In general, where such flux across cells takes place, membranes must present differing activity towards metals at the opposite side of the cell to produce net influx/efflux (Funder et al., 1978; Kaplan and Lutsenko, 2009). Small metallo-chaperones or specific transport proteins circulate in the body fluids and determines the destination of the metals they ferry; albumin (M_{wt} 69kDa) ferries Cu^{2+} is mainly from the gut to the liver, while ferrying Zn^{2+} is mainly from the liver to other tissues; however, transferring (M_{wt} 80kDa) has a binding capacity of $2Fe^{3+} + 2CO_3^{2-}$ whereas ferritin (M_{wt} 440kDa) contains a high proportion of bound metal, such as (FeO·OH)8 FeO·OPO3H2, and this inner iron micellar core can have a variable number of iron atoms (mostly as Fe^{3+}) associated with it, up to a maximum of ~4500

(Linder et al., 1998; Griffiths et al., 1999; Finney and O'Halloran, 2003; Knutson, 2007; Prohaska, 2008; Kaplan and Lutsenko, 2009; Knovich et al., 2009).

Fig.2: Models of metal transport systems through biological membrane.

Channel proteins utilize chemical or electrical potential to drive the substrate [S] through a specific pore in the lipid bilayer membrane. The substrate is denoted by $[S]_e$ for extracellular and $[S]_i$ for intracellular concentration. Carrier proteins undergo a conformational change to facilitate the movement of ions across the membrane using concentration gradient of the substrate. A co-substrate can be driven along with a one-way flux (symport) or by coupling the movement of another cation in the opposite direction (antiport) like Ca^{2+} / Na^{+} exchange which sustains cell integrity. The major metals have specific enzymic ion-pumps, which couple metal transport to energy utilization, usually provided by adenosine triphosphate (ATP) hydrolysis to drive substrate against concentration gradient. In addition, protein-mediated transport systems display a relationship between rates of substrate flux as a function of its concetration that fits Michaelis-Menten equation (1913).

Adopted: Stein, W.D. (1990) Channels, Carriers, and Pumps: An Introduction to Membrane Transport. New York, NY: Academic Press; Hajjawi,O.S. (2013b) "Human red blood cells-2", Am. J. Life Sciences, vol.1 (5),pp.215-227.



Since metal ions can be both essential and toxic, a delicate homeostasis balance must be maintained to sustain intracellular metal ion concentration within the level range that serves for optimal activity (Finney. and O'Halloran, 2003). Therefore, control of metal ion concentration is crucially important to retard showing toxic effects when they are in excess (Williams, 1970; Ellenhorn and Barceloux, 1988; Hardman et al., 2001; Singh et al., 2011). Hence, there is a particular hazard that metals compete for cation binding sites, and thus interfere with each other's functions (Williams, 1982; Curtis and Liu, 2013). Homeostasis is achieved by active transport and storage mechanisms; and buffering action of small molecules is another factor to reduce free metal ion concentrations (Fu et al., 2013). The major metal ions Ca^{2+} and Mg^{2+} are substantially buffered, while Na and K remain almost free; minor metals which are buffered by metabolites such as amino acids are capable of competing with major metals and with each other for binding sites (Williams, 1970; 1982; Finney and O'Halloran, 2003).

There are reserves of some metals in the body, such as Co^{2+} (vitamin B_{12} in the liver), Ca^{2+} (in bones), Mn^{2+} (in liver, kidneys and bones) and Fe^{2+} (in haemoglobin, liver and myoglobin) (Emsley, 2001). The divalent metal-ion transporter-1 (DMT1) is the major transporter responsible for intestine, erythroid cells, kidneys, lungs, brain, testis and thymus absorption of Fe^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, and Mn^{2+} (Eide,2004; Mackenzie and Hediger, 2004; Nadadur et al., 2008).

Ferrochelatasethe (M_{wt} 41kDa), which is the last enzyme in the heme pathway, catalyzes the insertion of Fe^{2+} into protoporphyrin IX to form haem Fe-protoheme IX though it can occur spontaneously; human ferrochelatase is a homodimeric, inner mitochondrial membrane-associated enzyme that possesses an essential [$2Fe^{2+}$-$2S^{-2}$] cluster (Straka et al., 1991; Magness et al., 2000; Medlock et al., 2007).

The movement of the major metal ions across cell membranes is associated with those of anions and cations, because there is a complex relationship between pH, transmembrane potential and the various extracellular and intracellular concentrations of constituents (Ellory and Lew, 1977; Hajjawi, 2013b). As shown in Table 3, the cell has a universal need to efflux Na^+ from the intracellular compartment in order to accumulate K^+, but the membrane depends on ATPase to facilitate this cationic exchange in the ratio of $3Na^+:2K^+$, Consuming 1 ATP (Hajjawi, 2012a).

During the early days of biomarker research in environmental studies two decades or so ago, molecular and diagnostic biochemical biomarkers were considered as the most promising tool for such purposes; catalase [EC 1.11.1.6], glutathione-s-transferase [EC 2.5.1.18] and cholinesterase [EC 3.1.1.8] are however the enzymes which are often utilized (Novelli et al., 1995; Jemec et al., 2010). Since diagnostics of pneumoconioses, neuropathies, hepatorenal degeneration, Alzheimer, Parkinson, various cancers and other more complex diseases in the future have often linked to chronic occupational exposure to metal dust, the substantial body of experience obtained with biochemical biomarkers would be exploited into new trends in genomic, proteomic, metabolomic and lipidomic biomarkers that would be able to measure exposure, effect and susceptibility of metal ions for human health in terms of toxicology of nanometals, antioxidant defense mechanism, metal ions deficiency on cell death in the brain, cytotoxicity, metal ions ligands , biomedical implant materials, cancer and others (Schober et al., 2006; CONTAM, 2009; Diez, 2009; Dopp et al., 2010; Plum et al., 2010; Silins and Högberg, 2011). However, it is crucial to generate an inclusive understanding of Table 1 dietary metals homeostasis for a better health-sustaining prospects.

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