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Biochemistry of metal absorption in Human Body: Reference to check Impact of Nano Particles on Human Being

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Abstract- Living is made comfortable by continues and the enormous advancement of Science and Technology so far. Nano technology is now days a favorite tool for technologists from academia as well as industrial sector. Nano particles were present in earlier days also, but up to limited extent. The prevailing use of Nano particles now days, to serve almost every sector of human life, would result in to increased concentration of Nano particles in the environment; eventually to term them as a pollutant. Metal absorption in human body is a very complicated phenomenon itself. For trace element absorption a protein, namely, metallothionein is responsible. Metal particles, when enter the human body, are likely to accumulate in kidney, lungs or brain. Greater surface to volume ratio of Nano particles makes them highly reactive and may act as catalyst even. This gives a call to understand the biochemistry behind metal absorption in human body and to define a strategy for the use and production of nano particles for their discrete use.

Index Terms- Nanotechnology, Nanoparticles, Biochemistry of metal absorption in human body

I. Introduction

Nano has become a very favorite term that each of us, -from academia, industry or research institutes, coin it frequently during routine conversations. Nano particles have high surface to volume ratio i.e. they contain high number of atoms per unit volume. As the size reduces, the proportion of atoms found at the surface increases relative to the proportion inside its volume. This increases reactivity of material at nano level. The nano particles are more reactive and hence adverse effect caused by them at lower dose level is greater than their fine counterparts. Due to expanding use of nano particles and commercialization of nano technology products, exposure of the environment and humans to nano particles is bound to increase and an evaluation of their potential toxicity is highly essential. Once in the system, the metal nanoparticles accumulate in different organs because the body has no way to eliminate them. And because they are so small, they can go everywhere in the body, even through cells, and may interfere with sub-cellular mechanisms [1-3].

II. Which are the metals present in human body?

Common Elements present in Animal and Human body

Animals and humans have similar evolutionary backgrounds. Specific elements play critical roles in the structures of proteins and the activities of enzymes. The purpose of this page is to outline some of the uses of elements in the structure of animals and humans and to illustrate why these elements are essential in the body and for optimal health.

III. Macro Elements

- **Calcium (Ca)** Structure of bone and teeth.
- **Phosphorous (Ph)** Structure of bone and teeth. Required for ATP, the energy carrier in animals.
- **Magnesium (Mg)** Important in bone structure. Deficiency results in tetany (muscle spasms) and can lead to a calcium deficiency.
- **Sodium (Na)** Major electrolyte of blood and extracellular fluid. Required for maintenance of pH and osmotic balance.
- **Potassium (K)** Major electrolyte of blood and intracellular fluid. Required for maintenance of pH and osmotic balance.
- **Chlorine (Cl)** Major electrolyte of blood and extracellular and intracellular fluid. Required for maintenance of pH and osmotic balance.
- **Sulfur (S)** Element of the essential amino acids **methionine** and **cysteine**. Contained in the vitamins thiamin and biotin. As part of glutathione it is required for detoxification. Poor growth due to reduced protein synthesis and lower glutathione levels potentially increasing oxidative or xenobiotic damage are consequences of low sulfur and methionine and/or cysteine intake.

IV. Micro Elements

- **Iron (Fe)** Contained in **hemoglobin** and **myoglobin** which are required for oxygen transport in the body. Part of the **cytochrome p450** family of enzymes. Anemia is the primary consequence of iron deficiency. Excess iron levels can enlarge the liver, may provoke diabetes and cardiac falurer. The genetic disease **hemochromatosis** results from excess iron absorption. Similar symptoms can be produced through excessive transfusions required for the treatment of other diseases.
- **Copper (Cu)** Contained in enzymes of the **ferroxidase** (ceruloplasmin?) system which regulates iron transport and facilitates release from storage. A structural element

in the enzymes **tyrosinase**, **cytochrome c oxidase**, **ascorbic acid oxidase**, **amine oxidases**, and the antioxidant enzyme **copper zinc superoxide dismutase**. A copper deficiency can result in anemia from reduced ferroxidase function. Excess copper levels cause liver malfunction and are associated with genetic disorder **Wilson's Disease**

- **Manganese (Mn)** Major component of the mitochondrial antioxidant enzyme **manganese superoxide dismutase**. A manganese deficiency can lead to improper bone formation and reproductive disorders. An excess of manganese can lead to poor iron absorption.
- **Iodine (I)** Required for production of thyroxine which plays an important role in metabolic rate. Deficient or excessive iodine intake can cause goiter (an enlarged thyroid gland).
- **Zinc (Zn)** Important for reproductive function due to its use in FSH (follicle stimulating hormone) and LH (leutinizing hormone). Required for DNA binding of zinc finger proteins which regulate a variety of activities. A component of the enzymes **alcohol dehydrogenase**, **lactic dehydrogenase carbonic anhydrase**, **ribonuclease**, **DNA Polymerase** and the antioxidant **copper zinc superoxide dismutase**. An excess of zinc may cause anemia or reduced bone formation.
- **Selenium (Se)** Contained in the antioxidant enzyme **glutathione peroxidase** and **heme oxidase**. Deficiency results in oxidative membrane damage with different effects in different species. Human deficiency causes cardiomyopathy (heart damage) and is known as Keshan's disease.
- **Fluorine (Fl)** Constituent of bones and teeth. Important for tooth development and prevention of dental caries. Derives from water, tea, and fish.
- **Cobolt (Co)** Contained in vitamin B12. An excess may cause cardiac failure.
- **Molybdenum (Mo)** Contained in the enzyme **xanthine oxidase**. Required for the excretion of nitrogen in uric acid in birds. An excess can cause diarrhea and growth reduction.
- **Chromium (Cr)** A cofactor in the regulation of sugar levels. Chromium deficiency may cause hyperglycemia (elevated blood sugar) and glucosuria (glucose in the urine).

Other Elements

Rats have been shown to have improved growth on diets which contain other micro nutrients. These include:

- **Lead (Pb)**
- **Nickel (Ni)**
- **Silicon (Si)**
- **Vanadium (Vn)**

These elements are all toxic at high levels.

At elevated levels, heavy metals can cause health problems.

Some metals, such as iron, chromium and copper, are needed in small quantities to keep people and animals healthy. Problems can occur with these metals if the body receives too much of them. Heavy metals such as lead and mercury are never desirable in any amount. Once inside our bodies different metals can build up in different body parts, including the kidney, liver and spleen.

The metal particles (ion or molecule) are normally found in human body. Metals are entering to the human body through food (vegetable, Spinach - iron); air (inhalation of ultrafine particles) and water (ground water contains dissolved metal salts and minerals from earth strata). Few of the metals entered, are essential for life; whereas, others are useless and even may be life threatening. However through following mechanism they remain accumulated in the various parts like kidney, liver, brain, blood of human body.

V. Entry of Metals to Human Body

1. Digestive system: Entry of these metals and the nano materials to human body can take place through digestive system. Titanium Dioxide is used in cosmetics and vitamins and other drugs as a filler to construct tablets. But it is also used in skimmed milk, cheeses, yogurts, mayonnaise, chocolate marshmallows, manufactured fast foods, tomato ketchup. It is fed to animals that humans eat.

Titanium is used as food additive in European countries as a food coloring, it has E number E171. Human digestive system starts with mouth and ends with anus (Fig 1). In mouth mechanical disintegration of food takes place. Then it enters esophagus and liver then stomach. Along the way the necessary elements are absorbed.

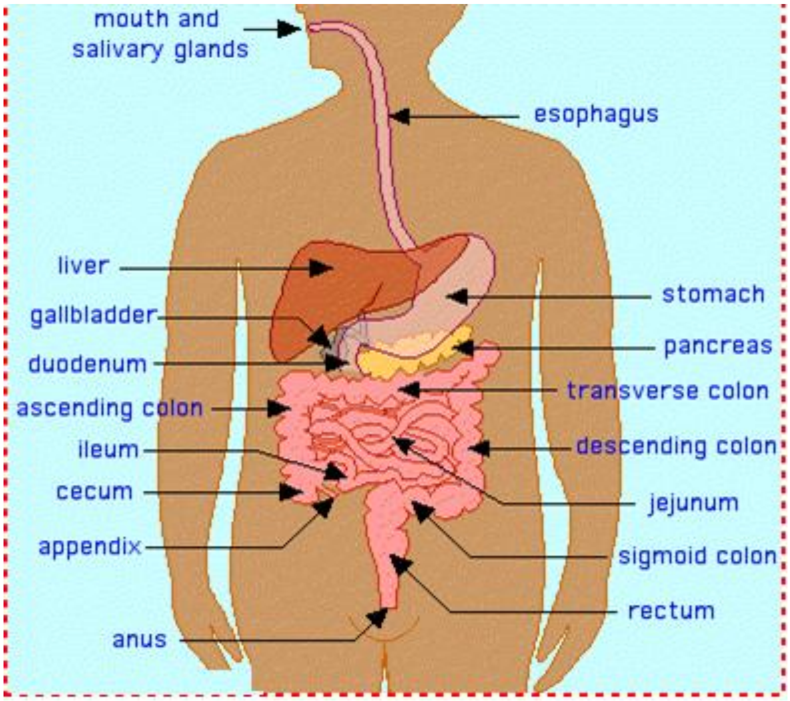

Fig. 1 Human Digestive System

Mechanism of absorption: Essential Metals are absorbed by the human body by developing homeostasis. Gastrointestinal absorption of trace and toxic elements is known to occur in three different phases:

1. The intraluminal phase with its chemical reactions and interaction with the content of stomach and intestine.
2. The translocation phase i.e. diffusion of trace elements across the cell membrane of the enterocytes and
3. Mobilization phase including mobilization and transport of the intracellular elements in to the blood stream or their sequestration back into the intestinal lumen.

The constant concentration of necessary metals in human body is maintained by the mechanism of homeostasis. E.g. iron absorption (Fig.2).

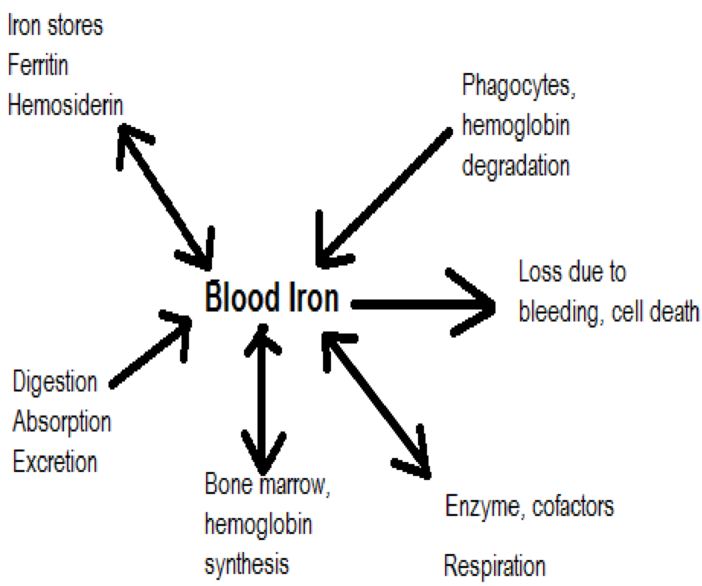

Fig.2 Homeostasis of iron in blood

VI. Entry of Metals and Nanoparticles Through Respiration

The metal processing units are the sites where very fine particles of metal are floating as particulate matter in and around the units in close vicinity. Similarly the nano material processing units are rich with ultrafine, light weight nano particles floating in and out the units or laboratories and are likely to get inhaled by the workers over there. Titanium dioxide dust, when inhaled, has been classified by the International Agency for Research on Cancer (IARC) as an IARC Group 2B carcinogen, meaning it is possibly carcinogenic to humans [4].

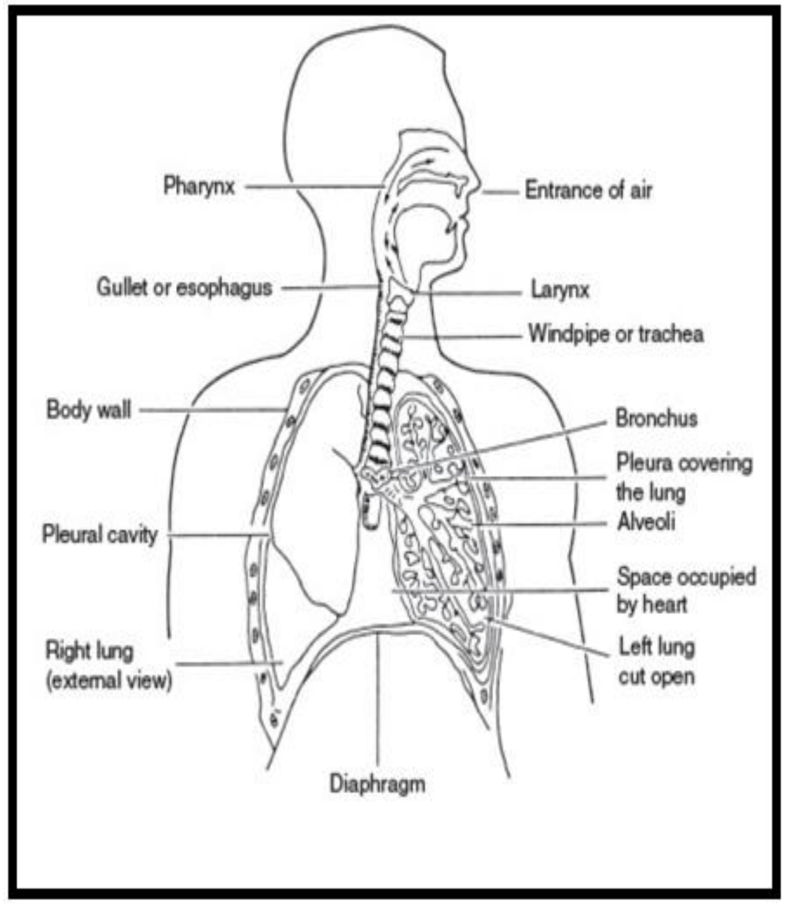

Fig.3 Human respiratory system

Excretion: Non- absorbed and Waste material (solid, liquid and gaseous form) is removed from the body. However in case of nanoparticles, it is observed that they are cytotoxic, can enter the blood stream and even can damage the DNA [5]. Studies on animals have investigated damage to the lungs (Fig. 3) by nano-TiO_2 varying from species to species of guineapigs [6]. The toxicity of nanoparticles is found to be dose dependent when the animal study was followed. Even the effect of size and shape is also pronounced one. In their study report, Ge et al [7] relates the toxicity reduction to bio-compatibility of the CNTs. By using both experimental and theoretical approaches they investigated the interactions of single-wall carbon nanotubes (SWCNTs) with human serum proteins, and find that morphology as well as chemical conformation played vital role in defining absorptivity of the CNTs. Sustainable energy harvesting, such as solar energy, depends increasingly on nanotechnology components. The principles of photovoltaic units and the toxicological aspects of its principal components, namely fullerenes and carbon nanotubes are well studied and discussed by Sergio Manzetti, Otto Andersen [8].

Accumulation: Non-absorbed and non-excreted material remains in the body and may get bio-accumulated in organs like kidney, liver, epithelial cells, and olfactory nerves. Biocidal effects and cellular internalization of ZnO nanoparticles on Escherichia coli bacteria are well studied by Brayner et al [9] in their study they used di(ethylene glycol) as medium to interact Zn nanoparticles with gram negative bacteria. The E. coli cells after contact with DEG and ZnO were damaged showing a Gram-negative triple membrane disorganization. This behavior causes the increase of membrane permeability leading to accumulation of ZnO nanoparticles in the bacterial membrane and also cellular internalization of these nanoparticles.

Metal Human body interactions: There are environmental (water, air, soil, dust), occupational, medicinal and dietary sources of metal exposure. All the metals are cytotoxicity (ability to inactivate microbes by rupturing the cell wall). Few of them are beneficial to human bioactivity whereas most of them are neither beneficial nor essential to the human. The metals might be carcinogenic [10] for longer exposure of human to them (Table 1).

Table 1 Classification of metals based on characteristics of health effects

Nutritionally essential Metals	Metals with possible beneficial effects	Metals with no known beneficial effects	Metals with Toxic effects
Cobalt	Boron	Aluminum	Arsenic
Chromium III	Nickel	Antimony	Cadmium
Copper	Silicon	Barium	Lead
Iron	Vanadium	Beryllium	Mercury
Manganese		Silver	Beryllium
Molybdenum		Strontium	Nickel
Selenium		Thallium	
Zinc			

Chemical speciation has an impact on solubility, bioavailability, and persistence of metals and metal compounds in the environment; e.g. solubility is one of the major factors influencing bioavailability and absorption of metal and metal compounds.

Human body response to the metals and inorganic metal compounds: The human body responds differently to the inorganic materials. Table No. 2 reports the typical responses of human body to the metals.

Table 2 Classification of metals based on characteristics of health effects

Interaction	**Response**
Metabolism	It is limited to change in oxidation state, transition and pH alterations.
Presence	Sequestered, bound to specific plasma or tissue proteins or bone
Elimination	Being hydrophilic, eliminated in urine and bile
Absorption	Being in ionized state, membrane transport is the mean for tissue uptake.

Absorption of organic xenobiotics in the gastrointestinal track is favored by the lipid nature of intestinal cell membrane. Metals appear to diffuse through the outer surface of protein filament of the stratum conium which is hydrated; whereas lipophilic non polar organic molecules diffuse through the lipid matrix between the protein filaments [11].

Mechanism of metal absorption: Metallothioneins are a group of low molecular weight (aprrox. 6000 Daltons) proteins, rich in sulfydryl groups that serve as a legend for several essential and non essential metals. Metal absorption varies with its affinity towards the metallothioniens as researched by [12]. Table No. 3 enlist the metals and metal absorbing proteins.

Table 3 Metal selective metallothioneins

Metal	**Metallothionein Protein**	**Action**
Iron, Al, Mn	Transferrin, - glycoprotein	Transportation of Fe across cell membrane by binding with iron through plasma
Iron	Ferritin	Storage
Copper	Ceruloplasmin, -glycoprotein	Conversion of ferrous to ferric iron for transport using transferring
Lead	Lead binding protein	Blanketing of Pb in kidney and liver [13]
Metals	Membrane carrier Protein	Transport (multi metal specific) [14]

Replacement of essential metals during absorption with non-essential metals is possible. e.g. lead replaces zinc in hem synthesis by inhibiting the function of hem synthesizing enzyme [13]. Diminished iron absorption is observed in the presence of zinc. Substitution of calcium by lead results in toxicity of several vital enzyme systems in central nervous system [15, 16]. Arsenate replaces phosphate in mitochondria impairing the synthesis of ATP and energy metabolism.

Many of the processes controlling the disposition of metals are intrinsically capacity limited and highly specific. This makes it necessary to understand physiology well enough to model these processes and method to estimate binding constant. Another overarching theme is that metal – metal interactions of multiple types. (e.g. competition antagonism and synergism as well as essential – nonessential interactions) commonly occur at multiple points during the process of absorption, distribution, metabolism and excretion.

VII. Conclusion

As mentioned in the introductory section of this paper, nano particles are highly reactive species with subatomic sizes i.e. easy to enter through breathing and along with food. Like skin, the gastro intestinal track and the lungs are in direct contact with the environment. Nano particles like Ti or Zn oxides are used in sunscreen lotions. CNTs and fullerence are the members of electronic industries. Nano particles from hair dye (pigments) accumulate around the hair roots. During hair growth, these follicles are opened and in turn provide a route for nano particles to reach dipper layers. No uptake into the blood through healthy skin has yet been reported. Animal experiments show that nano particles can cross the air blood tissue barrier and thus enter in to the body circulatory system. As homeostasis is significant to retain or omit the metals from human body and the metal – metal interactions are of multiple types, it becomes necessary to understand biochemistry of metal absorption, retention, excretion and bio-accumulation to understand the effects of nanoparticles over human body. Thus it can be said that the regulatory strategy over use of nanomaterials, till the fatality of nanomaterials in environment is unknown, is highly necessary.

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