CONSIDERATIONS REGARDING THE IMPLICATIONS OF BIOMETALS IN MEDICINE

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Abstract: *Many diseases are associated with changes in the concentrations of the metal ions from the tissues or body fluids. Complex control systems supervise and maintain the metalic ions in normal concentrations in the body. Influencing the systems responsible for the control of metal ions leads to illnesses sometimes with a genetic trait. In the papers are presented aspects the biological role of the metal ions and the possible applications of the biometals in medicine.*

Keywords: biometals, applications, medicine

1. INTRODUCTION

The role of metals in the body can be considered in terms of surplus (poisoning), disturbance in the control systems (metabolic disorders), failure (illness, sometimes genetic trait). Metal poisoning represents the effect of the presence of excess metal ions useful in normal concentrations, but pests in surplus or body of foreign metal ions. For example, the poisoning with alkaline cations or earth - alkaline influence the osmotic balance.

The best known are accidental poisonings, professionals, with lead, mercury, iron etc. The presence of metal ions are harmful by removing the normal metal ions, connected at the centers of the proteins, causing changes in the efficiency of the enzymes or destroying the celular membrane and with it causing losses in the transport properties. Lead, mercury and arsenic displaces copper and zinc from complex biological combinations [1].

The modification of the concentrations of the biometals in the body takes place due to the disturbance of the systems that control their concentration. For example, the copper concentration increases several times during a malfunction of the liver (epidemic hepatitis, cirrhosis) and during the manifestations of other diseases like nephritis, psoriasis, leukemia, etc. Therefore, changes of the concentrations of copper ions in the body can be used in establishing the diagnosis and tracking the treatment of the dominant disease.

Different pats of the viruses have the capacity of generating chelates. Introducing a metal complexed ion in the vicinity of a virus, creates the possibility that the virus replace the complex ligands, by forming a new complex, non-pathogenic or less pathogenic [2].

Biometals from the body are contained in large amounts of food and water. Only in exceptional cases are needed special preparations that contain one or more bioelements in assimilable in the live body. If these bioelements fall below a certain level in the body, it gets sick. Iron defficiency leads to anemia, the copper defficiency leads to the destructions of blood vessels, the zinc defficiency decreases suddenly the numerous enzymes catalysts in the hydrolytic processes, the magnesium defficiency leads to destructions of ribosomes.

The excess in bioelements can lead to serious illnesses. It appears due to the disruption of the system that regulates the bioelements concentration. For example, excess copper in the liver, brain or kidneys give Wilson disease, of whose symptoms varies depending of the metal concentration, a disease that is genetically transmited, because of a big excess of iron in the body siderosis occurs [3].

At the excess of calcium appears organic precipitations in the form of stones having as an effect their deposition on the blood vessels walls.

A partcular interest is the influence of excess potassium ions on heart function. His excess outside the cell, duble than normal, lead to severe metabolic disorders and even death. On the other hand, increasing the concentrations of potassium ions in the interior of the cell does not lead to serious consequences [4].

Bioanorganic chemistry discusses the interactions with biosystems not only life metals, but also other metals. In this connections, a special interest it represents the study of the poisong mechanism at a molecular system with metals like: mercury, arsenic, bismuth, lead and beryllium. The first four metals (Hg, As, Bi, Pb) blocks the -SH groups of the proteins or eliminates from the enzyme active metal ions like Cu^{2+} or Zn^{2+}. Beryllium blocks some of the hydrolytic enzymes and are bind tighly, by complexing with nucleic acids [5].

Ions like K^{+}, Ca^{2+} and Mg^{2+} play a very important roel in medicine, the most important being their effect over cardiac glycosides. If there appears an excess of cardiac glycosides, there can take place a full stop of heart activity and sometimes even the death of the body. While introducing in the blood plasma the K^{+} and Mg^{2+} ions the activity of cardiac glycosides decreases. The Ca^{2+} ions increase the activity of cardiac glycosides. This fact can be decreased by lowering the calcium concentration that can be obtained, for example,by introducing in the biological fluid the EDTA [10].

Some coordinative compounds can be used like antibacterial preparations and anti-fungus, this kind of eventual action could also have some potential ligands. The quinolinoxy complex of Fe (III) have a very strong antibacterial action [13]. The activity of the tiacetanoza increases suddenly in the presence of the copper ions, probably because of the forming of coordinate compounds that can pass through the biological membranes. Tetracycline destroys the bacteria ribosome by connecting the Mg^{2+} [12]. The proliferation and growing of the microorganisms has been stopped by tetracycline, that can be reactivated by adding in the organism the magnesium ions.

2. ASPECTS REGARDING THE IMPLICATIONS OF BIOMETALS IN MEDICINE THE IMPLICATIONS OF THE BIOMETALS IN THE DRUGS ACTIVITY

Metal complexes play a very important role in the drugs activity. Generally, the drugs establish interactions at a cellular level. Many drugs substances act like chelating agents. The correlation of the activity of a drug with their ligand properties, in vitro, is very difficult and it was proven that in this situation the drugs does not concurate efficiently with other ligands, and even *in vivo*, it controls and inhibates the enzymes activity, by chelatisation of metal ions. Metal complexes play an important role in drugs activity. Generally, drugs establishes interactions in the cell. Using drugs that are proven to be effective is prevented, sometimes, by the appearance of the secondary effects or the one made by its metabolites, processes which can be explained, partially, through chelating reactions. Also through their properties to form complexes, absorption in the body can be explained, different properties depend of several factors (the pH of the biological medium), drug interactions, tolerance or intolerance of the body etc. It should be noted that many medicinal preparations contain ligands that interact specifically with some metals or metal groups [9,11,14,15].

The easiest, at a molecular level, the substances actions that connect selectively the toxic metal ions or the harmful excess in biometals can be explained. Substances of this kind are called detoxifying and these must accomplish at least three requirements:

- dis-intoxicants and their coordinative compounds with metal ions must be non-toxic;
- coordination compound of the metal ion with the dis-intoxicant must be more stable than the compound of the metal ion with the corresponding group of the apoprotein;
- coordination compound of the metal ion with the dis-intoxicant must passouwardly through the cell membranes, that is oil-soluble [1,6].

Applications of the most important dis-intoxicants:

- Dimercaprol eliminates from the body the As, Te, Tl, Hg, Au (but not the Pb);
- Depenicicilamina forms a coordinative compound very stable with the copper ions; it is being used at treating Wilson disease;
- Etilendiaminotetraacetat ion forms stable coordinative compounds with the lead and vanadium ions and it eliminats them from the body;
- Aurintricarboxilat ion forms stable coodinative compounds with Be^{2+} and it is being used for elimanting the berrilium from the poisoned body.

The actions of the numerous drugs preparations and of the different dis-intoxicants it is based on blocking the active centers of the metal-enzymes, CN^- bloks the respiratory enzymes by attaching to the iron located in central position.The disulfiramul blocks the copper iron from an enzyme that catalyses the oxidation of the alcohol and it is being used in treating alcoholism. Introducing it in the body makes thealcohol to oxydate until arriving to acetaldehyde, that is being stored in the body and its consumption gives unpleasant sensations and sometimes even painful ones [6,7].

Redox biosystems with transitional metal ions and their biological role

A) Iron-metal-proteins. Hemoglobines, together with the mioglobine, represents 98% from the body proteins. Each adult contains a kilo of hemoglobin regenerated at everuy 3-4 months. Hemaproteins are implied in two processes: essentials to life: (a) photosynthethis, converting solar energy in potential energy in vegetals, and (b) cellular respirations, converting this energy, during aerobic oxidations, in dynamic energy of ATP type [4,5].

Hemoglobines are cromoproteide porphryn, core componets of the red cells from the blood of vertebrates, having a very important function in the transport of gases (O_2 şi CO_2) between lungs and tissues. From a structural point of view hemoglobin is formed from a protein compound, globin, with basic character and a heme prosthetic called heme. The structure of the heme was established both through gradual degradation of the molecule and the identifications of the products resulted also through synthesis. The heme is formed from protoporphyn and in his center there is a Fe^{2+} iron. The main function of the hemoglobin (Hb) is to carry molecular oxygen from lungs to tissues. The heme it can be combined reversibly with the oxygen forming a dissociable, oxyhemoglobin. The direction of the equilibrium of this reaction depends of the partial pressure of the oxygen. For example, in the lungs, at a big partial pressure of the oxygen, are being set 19,6 ml of oxygen in each 100 ml of blood (the equilibrium being shifted to the right) and in the tissues, at the level of the capillaries vessels, at a small pressure of the oxygen, the equilibriumis being shifted in the for the purpose of decomposition of oxyhemoglobin. Thus, for every 100 ml of blood is issued 7-9 ml of oxygen to tissues The released hemoglobin resume its role of transporter of oxygen. Fixing the oxygen takes place through coordinative binding to iron, without modifying the iron

valence. In the absence of globin the heme cannot bind the oxygen. Hemoglobin reacts irreversibly with the carbon oxide by forming carboxyhemoglobin. The affinity of hemoglobin for CO is 210 bigger than the affinity for O_2. Thus, in the presence of CO in the air we breathe, hemoglobin does not bind anymore the oxygen but the carbon oxide, this being the reason for the harmfulness of the CO, which can cause death through asphyxiation if more than 50% of the hemoglobin is blcoked under the shape of carboxyhemoglobin [5,8].

B) Cobalamina (Vitamin B12) is essential for animals and men life. The vegetable kingdom it can be found in low quantity. It can be extracted in a big quantity from the waste waters from the production of the penicilin, streptomycin etc. Vitamin B12 it can be found in the animal body and in microorganisms having the role of growing. In the animal body it can be found in the liver, kidney, heart and in adrenal glands. The microorganisms from the rumen and intestine synthesize vitamin B12. The biochemical and physiological role of the vitamin B12 it is accomplished by the coenzyme B12 that is being synthesized in the presence of a specific enzyme B12-synthase. Vitamin B12 participates as a coenzyme in the processes of carboxylation, in the biosynthesis of the heme, in the biosynthesis of the DNA, in the biosynthesis of proteins and lipids. It has a very important role in the process of hemetopoetic by preventing anemia. Vitamin B12 is a growth factor for the young bodies, promotes cell division, and maintains the integrity of the nerve cell. Vitamin B12 produces anemia, demineralization of the nervous system and delays in the growth of young bodies.

In avitaminosis, many cells do not divide, remain big, especially in the spinal cord and thus it is produced the pernicious anemia. The number of leukocytes is reduced and gigantic granulocytes appear. Avitaminosis occurs, generally, from poor absorption in the body. The daily requirement of vitamin B12 is 30 mg [3,8].

Bio-inorganic compounds with a potential carcinogenic activity

Certain chemical substances have a potential carcinogenic and anticancer activity. It was established the compatibility between the anticancer activity and another two important properties of the drugs preparations:

- the antibacterial activity and the antivirus activity;
- the ability to stop DNA synthesis.

Substances different as chemical structure, present a selectivity in relation to the action over different forms of cancer. The invetigation of the coordinative compounds of the metals from the 4th perios (transition metals, 3d) has shown that only some of them can have an effective action in treating cancer. From the simple chlorides (non-cmplex) some activity presents only $ZnCl_2$ [7]. The ability to inhibit the cancer tumors have the salts of some carboxylic acids with a low toxicity (for example the Mn malonate). The positive results regarding the cancerostatic activity have been obtained when using some preparations with Cu^{2+}. The Cu^{2+} compounds with cysteine and feniltioureea have a potential cancero static activity. The coordinative compounds $[Cr(NH_3)_4C_2O_4]$ and $[Cr(NH_3)_2(C_2O_4)_2]$., in which both the cation and also the anion are complex ions, weakly inhibit some cancer forms. The coordinative compounds of Ir(III) does not have, practically, a anticancer activity, although after their irradiation with UV light it might appear such an activity. The complex $[Ru(NH_3)_3]Cl_3$ actions over Escherichia Coli approxymately in the same way as $[Pt(NH_3)_2]Cl_2$, but does not present an anticancer activity [2,6].

3. CONCLUSIONS

Biometals "stored" in the body refreshes itself in a systematic way. If bioelements fall below a certain level in the body, illnesses are being produced as the excess in bioelements can lead to serious illnesses. A number of complexes with metals from the platinium group are known for their bactericidal and bacteriostatic effects and the anti-tumor efects of some of them, to a wide range of tumors, being used successfully in cancer chemotherapy at humans.

The anticancer effects of the coordinative compounds of the transition metal are being substantiated by the investigations results regarding the mechanism of action of anticancer preparations. Some of these being that for stopping the growth of the cancer tumor is necessary to block the enzyme activity that normally lead to a fast growth of the tumor.

The excess of one of the metals useful in the organism can give poisoning, impaired sontrol system can be followed by disturbances of the metabolism, and the insufficient concentrations, followed by illnesses. The control exercised by the metal ions over some biological processes highlights the dependence of life and organic alike.

The use of bio-inorganic chemistry in medicine is based primarly on the concentrations (and quanties) of metals in different tissues of the live bodies which function normally, and are maintained at a strict determined level, due to the rigorous control of the system consisting of proteins and hormones.

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