

Spectrum of application magnetite nanoparticles in medicine

Andrey N. Belousov

Laboratory of Applied Nanotechnology

pr. Lenina, 31-v, fl. 32

Kharkov, 61072 Ukraine

E-mail: anb@vlink.kharkov.ua

Web site: www.nanolab.com.ua

ABSTRACT

Nowadays nanotechnology as a new direction of science allows to develop therapeutic methods of the endogenous intoxication syndrome and to create a new class of biocompatible sorbents. In Ukraine first preparations of medical nanotechnology were produced and patented in 1998. These are "IKBB" intracorporeal biocorrector, magnet-controlled sorbent (MCS-B), and "Micromage-B". The preparations are based on colloid magnetite particles (Fe_3O_4) from 6 to 12 nm. Adsorption layer provides a high sorption activity to magnetite nanoparticles. Total activity of their sorption surface is 800 – 1200 m^2/g , magnetic field intensity produced by each particle is 300 - 400 kA/m, ζ – potential is – 19 mV. Each magnetite particle is a subdomain elementary magnetite of a sphere shape. The main biological action of nanotechnology preparations is direct to regulation of cell metabolism. Therapeutic effect of this preparation is based on the influence of adsorption process and of constant magnetic field that surrounds colloid magnetite particle on cellular and subcellular structures. Point of attack is surface proteins of cell membranes. Colloid magnetite particles modify composition of protein molecules thereby effecting transport of substances to a cell. Using magnet-controlled sorbent the method of extracorporeal hemocorrection on the whole is rather the method of effective and reliable way to activate natural processes of detoxication of organism, than the method of artificial detoxication. The absence of contraindication and incidental effects (haematic, haemodynamic, hormone, electrolytic, immune) creates real predisposition for using this method in intensive therapy of intoxication syndrome.

Keywords: magnetite nanoparticles; medical nanotechnology; regulation of cell metabolism; intensive therapy; intoxication syndrome.

The history of nanotechnology has begun not so long ago, only in 1959 when a Nobelist Richard Freyman delivered literally the following: As far as I know not a single physical or chemical law doesn't prevent us from changing relative position of atoms [10].

It has been almost 45 years since the speech of Richard Freyman in front of the Nobel Committee and since then the humanity has passed from words to deeds.

However, nanotechnology still stays the most mysterious and on the other hand the most prospective technology of the twentieth century. So far there is no an exhaustive definition of nanotechnology. By analogy with microtechnology we can say that technology operates with units about the size of a nanometre, i.e. with one billionth of a metre. This is a trace unit which is hundred times smaller than the length of a visible light wave and which is comparable with size of an atom. Therefore *a change from micro to nano is a qualitative change implying the switch from manipulation with*

substance to a separate atom manipulation, but not a quantitative one. Although not many researches or discoveries have been made in this field of science, most scientists believe that the revolution is to come soon. Nanotechnology is a real breakthrough in science and in life in general [9, 10].

Nowadays nanotechnology is at the beginning of its development; however it is clear already now that those tiny nanoparticles of size of one million of a pinhead provide great opportunities for various fields of medicine. According to the definition of R. Freyman, a leading scientist in this field, nanomedicine is "Monitoring, correcting, designing, and control over biological systems of a human being at molecular level with the help of nanodevices and nanostructures" [7].

In Ukraine first preparations of medical nanotechnology were produced and patented in 1998. These are "IKBB" intracorporeal biocorrector, magnet-controlled sorbent brand of "MCS-B", and "Micromage-B" [1-3].

The preparations are based on colloid magnetite particles (Fe_3O_4) from 6 to 12 nm. Adsorption layer provides a high sorption activity to magnetite nanoparticles. Total activity of their sorption surface is 800 – 1200 m^2/g , magnetic field intensity produced by each particle is 300 - 400 kA/m and ζ – potential is – 19 mV.

Extracorporeal hemocorrection method with application of magnet-controlled sorbent (MCS-B) has a significant pathogenetic advantage over the existing detoxication methods [4].

Some results of the sorption capacity of magnet-controlled sorbent in various biological environments are shown in the table 1.

The table 1 demonstrates the sorption activity of magnetite nanoparticles regarding heavy metal salts, nitrates, phenol, and passivity regarding the main electrolytes of blood plasma. This allows using magnet-controlled sorbent MCS-B for cleaning biological body liquids without a threat of electrolytic disorder.

It is also important to mention that magnet-controlled sorbent has not only a sorption effect but also an indirect effect caused by the influence of a constant magnetic field created by magnetite nanoparticles.

An important advantage of magnet-controlled sorbent MCS-B is that its sorption qualities are highly specific (selective) and that they have a big resemblance with molecular components of blood plasma which stimulate endogenous intoxication syndrome (fig.1).

Such selectivity of magnet-controlled sorbent creates prerequisites for indirect sanogenetic effects in the process of therapy.

A particular characteristic of the extracorporeal hemocorrection method with application of magnet-controlled sorbent is that, first of all this method is an

alternative not to a detoxication method but to a systemic nonspecific biological modulation.

Table 1.

Some data sorption activity of MCS-B * for a various sort of the substances which are taking place in biological liquid.

Substance	Biological liquid		
	H ₂ O	Plasma of blood	The blood
Phenol	1 mcg	0,05 mcg	0,05 mcg
Albumin		Absent	Absent
Creatinin		Absent	Absent
Urine	Absent	Absent	Absent
Cholesterol		10 mcg	10 mcg
Hormone T ₃		Absent	Absent
Cu	1,75 mcg	2,5 mcg	1 mcg
Ca ⁺⁺	Absent	Absent	Absent
K ⁺	Absent	Absent	Absent
Na ⁺	Absent	Absent	Absent
Cl ⁻	Absent	Absent	Absent
Mg	Absent	Absent	Absent
Zn	10 mcg	Absent	0,75 mcg
NaNO ₃	12,5 mcg	10 mcg	Absent
Cr	2 mcg	0,49 mcg	0,5 mcg
Pb	1,17 mcg	0,3 mcg	0,19 mcg
Cd	0,48 mcg	0,68 mcg	1,55 mcg
Ig A	500 mcmol	300 mcmol	250 mcmol
Ig M	200 mcmol	350 mcmol	250 mcmol
Ig G	Absent	200 mcmol	250 mcmol
Medinale	Absent	Absent	Absent
Thiopental Na	Absent	Absent	Absent

The note.* - at the rate of 30 mg MCS-B on 1cm³ liquids.

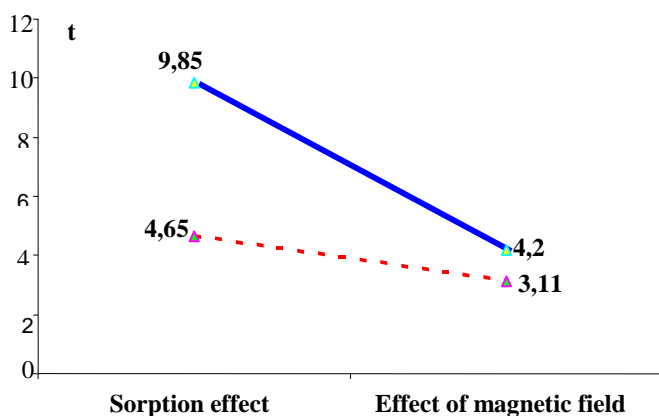


Fig.1. Complex certainty index of sorption and indirect effects of MCS-B:

— with toxemia patients; - - health people

The presence of a constant magnetic field around magnetite nanoparticles allows magnet-controlled sorbent to not only perform a selective adsorption of various substances like it is in magnetic phoresis, but also to actively effect intracellular biochemical processes.

Activating the process of oxyhemoglobin dissociation up to 1.5-2 times and raising output of blood oxygen to tissues, magnet-controlled sorbent restores bioelectric potential of

erythrocyte membranes, improves operation of blood cells, normalizes rheology and microcirculation (fig.2, 3).

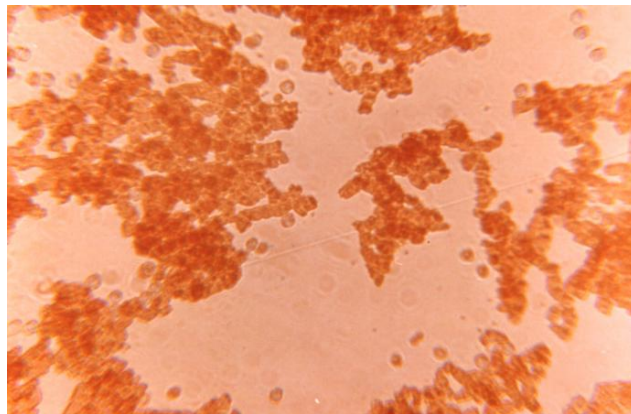


Fig. 2. Initial state of erythrocytes (marked sludge syndrome) of heparinized blood of a patient with K. with toxemia (x 200).

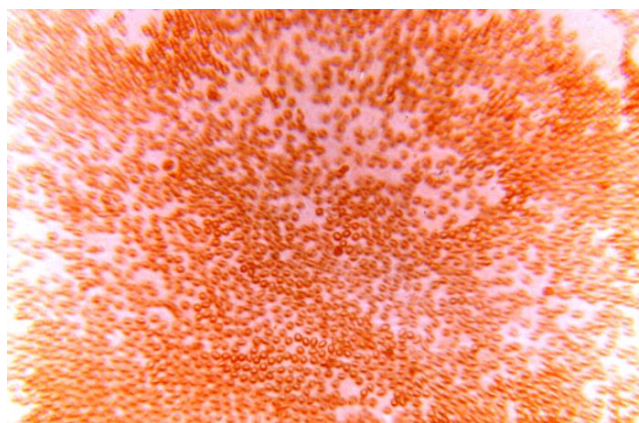


Fig. 3. State of erythrocytes (elimination of sludge syndrome) of heparinized blood of a patient with K. with toxemia after the treatment with magnetite nanoparticles in vitro (x 200).

Causing changes in hemoglobin buffer system, magnet-controlled sorbent exhaustively corrects pH and alkaline reserve of venous blood.

Improvement of metabolic disorders at cell level has been confirmed by results of electron microscope examination of the organs of reticuloendothelial system (liver, kidneys, lungs) in experiment.

Restoration of metabolic shifts of homeostasis, of physical and chemical characteristics of tissue structures, of balance between antiradical and proradical products characterizes a direct effect of magnet-controlled sorbent on free radical oxidation of lipids. This fact predetermines the main pathogenetic difference of the offered method from the other types of intensive therapy.

Correction of balance between antiradical and proradical products provides activity of magnet-controlled sorbent regarding pathogenic germs and condition of cellular immunity. As a result sensitivity of pathogenic germs (Staphylococcus aureus, Pseudomonas aeruginosa, Corynebacterium diphtheria, fungi of Candida type) to antibiotics increases in 2-3 times (table 2), and arises a pronounced bacteriostatic effect regarding pathogenic microflora.

Table 2.
Minimal depressing concentration of antibiotics regarding bacteria (mkg/ml) before and after MCS-B (M±m; n=20) exposure.

Antibiotic	S. aureus µg/ml		P. aeruginosa µg/ml	
	Control	MCS-B	Control	MCS-B
Carbenicillinum	9,0±0,6	3,0±0,4 P<0,001	≥100	60,0±10,5 P<0,05
Gentamicinum	5,0±0,8	2,0±0,9 P<0,05	12,0±1,2	4,0±1,3 P<0,05
Riphampicinum	9,0±1,3	3,0±0,7 P<0,001	14,0±1,4	5,0±1,5 P<0,001
Ofloxacinum	5,0±1,4	2,0±0,8 P>0,05	5,0±1,4	3,0±1,1 P>0,05

Note: P – accuracy of differences in comparison with control.

At the same time, MCS-B nanoparticles do not cause changes of biological characteristics of normal flora with exception of short term slight inhibition of growth qualities.

Selective bacteriostatic and antifungal effects, correction of immunologic disorder (increase in phagocytic activity of leucocytes and in phagocytosis completeness index, liquidation of immunoregulatory cells disbalance) complete the list of biological effects of magnet-controlled sorbent nanoparticles.

The principle of magnetic phoresis allows magnet-controlled sorbent nanoparticles to restore indices of protein (fig.4) and lipid blood fractions, to improve albumin-globulin coefficient, ESR, the level of lipid peroxidation products, regulate the quantity of hormones, of circulating immune complexes, and of microlymphocytotoxicity autoantibody.

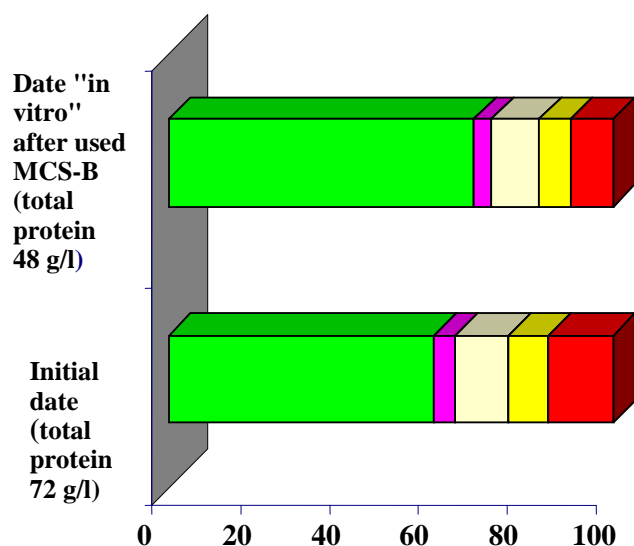


Fig. 4. Effect selective sorption protein fraction of blood by magnetite nanoparticles (MCS-B):



The proposed method of using MCS-B nanoparticles is technically simple and reliable in action. Absence of side effects (haemic, hemodynamic, electrolytic, hormonal, protein, lipid, immunological) creates real prerequisites for using this method in intensive therapy of patients with clinical cases of endogenous intoxication syndrome. The method can be used in the cases when the other methods of artificial detoxication are contraindicated (anaemia, hypoproteinemia, coagulopathy, thrombocytopenia) [5].

The second preparation of nanotechnology is its peroral form «Micromage-B». The preparation was registered by Ministry of Health of Ukraine in 1999 as a biologically active additive (registration № 5.08.07/1165 from 14.04.99). Therapeutic effect of this preparation is based on the influence of adsorption process and of constant magnetic field that surrounds colloid magnetite particle on cellular and subcellular structures.

Point of attack is surface proteins of cell membranes. Colloid magnetite particles modify composition of protein molecules thereby effecting transport of substances to a cell [6].

«Micromag-B» is a unique preparation for nonspecific modulation of metabolic processes. The preparation causes increase in adaptive potential mechanisms and in capabilities of cell organs; accelerates reparative processes at membrane and macromolecular levels.

In 2002 the author made a first attempt to systemize the results of the reasearch of nanotechnology preparations effect on cellular regulation mechanisms. It was proved that the presented magnetite nanoparticles carry out a role of a modulating factor of metabolic processes in leucocytes of healthy and ill people. They intensively modulate activity of an enzyme component of antioxidant system in erythrocytes of healthy and ill people.

Thus, we can say even now that the outlined positive progress in the research of nanotechnology preparations effect on cellular metabolism soon will allow us to find a key to understanding the cell apoptosis mechanisms, reasons of aging and thanatogenesis, and to discover a secret of longevity.

In conclusion we would like to mention that in spite of the optimistic prospects of nanotechnology development, in many countries an integral approach to the questions of nanotechnology has not been still formed. According to foreign authors at present there is a number of nanoprograms realization of which, in the end, will give good results. So far only big foreign companies can afford researches in this field as the experiments of this kind require proper finances. However, corporations do not spare money giving each year bigger sums of money on such researches [8]. Without a doubt, this field of science has great prospects in future.

REFERENCES

1. Belousov A.N. The treatment-prophylactic a product "Micromage-B": the State patent №30538A UA A 23L 1/304 (Ukraine). Declare 25.05.98. Published 15.11.00. Bull. № 6-11. - 3 p.
2. Belousov A.N. The sorbent for extracorporeal detoxycation of biological liquids: the State patent №24322A UA A61N2/00 (Ukraine). - Declare 19.06.97. Published 17.07.98. Bull. №7. - 4 p.

3. Belousov A.N. The method of synthesis a magnetic liquid for transport and controlled pharmacological preparations in organism: The State patent №14817A UA A61N2/00 (Ukraine). - Declare 21.06.96. Published 18.02.97. Bull. №2. - 3 p.
4. Belousov A.N. The method extracorporeal detoxycation of biological liquids: The State patent №24183A UA A61N2/00 (Ukraine). - Declare 19.06.97. Published 17.07.98. Bull. №7. - 3 p.
5. Belousov A.N. The extracorporeal hemocorrection with application of magnet-controlled sorbent in intensive therapy of syndrome intoxication in the patients with a pathology hepatopancreatoduodenum zones: The abstract dissertation of doctor medicine: 14.01.30. / The Dnepropetrovsk state of medical academy, 2004. - 40 p.
6. Belousov A.N. The influence magnetite – a preparation nanotechnology on metabolism of a cellular. // The Bulletin of problems of biology and medicine. Poltava, 2003. - №7. - P. 36-37.
7. <http://www.homestead.com/nanotechind/medical.html>
8. <http://www.nanoathome.org/>.
9. Lem St. Tajemnica chicskiego pokoju. – Kracow, 1996. – 98 p.
10. Phoenix C., Drexler E. "Safe exponential manufacturing", Nanotechnology 15(8): 869-872 (Aug 2004).