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Biological Activity of Metal Nanoparticles and Their Oxides and Their Effect on Bacterial Cells

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Abstract—Metal nanoparticles and their oxides are one prospective candidate for making a new class of antibacterial agents. Active interest in nanomaterials is caused by the fact that the transition to the nanodimensional level leads to a change in the fundamental properties of a substance that is connected with the display of so-called "quantum dimensional effects." The biological activity of metal nanoparticles and their oxides is caused by their small size; nanoparticles can approach a bioobject, interact with it, and contact it. In this review, the basic mechanisms of antibacterial activity of nanoparticles of silver, copper, nickel, and titanium oxide are considered; the metal nanoparticle biological activity dependence on their physicochemical properties is demonstrated. The necessity of studying the physicochemical parameters of metal nanoparticles and their oxides for the standardization of their further application as antibacterial agents is determined.

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INTRODUCTION

Due to the quick formation of resistance of microorganisms to antibiotics, it is necessary to find new alternative antimicrobial drugs [1, 2]. In this case, metals nanoparticles and their oxides are a prospective candidate for making a new class of antibacterial agents [3].

Interest in nanomaterials is caused by the fact that switching to the nanodimensional level leads to a change in the fundamental properties of a substance (magnet and optical characteristics, melt temperature, thermal capacity, and surface and catalytic activities) due to the display of so-called quantum dimensional effects [4, 5]. An increase in size is the reason for the change in state density in valence and conducting bands; it impacts magnet and electricity features caused by electron behavior. The "continuous" state density of features available in macroscale is changed to discrete levels, with distances between them depending on the size of the nanoparticles [6–8]. In this scope, material stops demonstrating the physical features of macrostate substances or could demonstrate it in a modified way [4, 9, 10].

The other main factor for physical characteristics of nanoparticles is an extended surface. It is the basic one for the predominance of surface phenomena. Due to uncompensated atom bonds on the surface of nanoparticles, the symmetry of intensity distribution is broken and it is the cause of an increase in free energy on the surface and the activation of adsorption processes and ionic and atomy exchanges [11]. The surface area of material in ultradispersity is more than the surface area of a substance with a high-range order. Due to it, completely new physical phenomena and features arise in a solid body. It is impossible to predict these phenomena and features because of the structure and features of massive substrate [4, 9, 10]. Nanoparticles have highly developed active surface and, as a result, high sorption capacity.

The biological activity of nanoparticles is determined by the small size of particles (less than 100 nm), which are the same as the sizes of cells, viruses, proteins, and DNA; nanoparticles can come close to a biological object, become compatible with it, and bind to it [12].

INFLUENCE OF METAL NANOPARTICLES AND THEIR OXIDES ON BACTERIAL CELLS

There has been a lot of research by Russian and foreign authors about mechanisms of the antibacterial activity of metal nanoparticles and their oxides. When D.N. Willams, et. al. (2006) researched the dynamics of *E. coli* growth in the presence of silicon oxide, iron oxide, and aurum nanoparticles, they came to the conclusion that these substances lead in changes of subcellular formations, such as genes or proteins.

Nanoparticles are very stable. Thus, they are not exposed to biological transformation and extracted from a cell, inducing stress in it and destroying it [13].

The precision mechanism of antibacterial activity of ultrafine particles of metal or their oxides is not clear at all. Nowadays, three hypothetical mechanisms obtain wide circulation:

1. Due to bacteria, a cell absorbs ions extracted by metal nanoparticles; ATP and DNA replication are violated [14].

2. Active oxygen forms generated by nanoparticles and metal ions are the reason for the oxidative damage of cellular structures [15].

3. The accumulation of nanoparticles in a bacterial membrane leads to a change in penetration due to the sustained release of lipopolyssacharide, membrane proteins, and intracellularly factors [16, 17].

A number of studies indicate that the interaction of nanoparticles with a bacterial cell occurs in stages. At the first (physical) stage, metal nanoparticles adsorb to surface of a microorganism due to resultant electrostatic pressure [18, 19]. After that, nanoparticles get inside. This is confirmed by submicroscopical researches [19, 20]. At the next stages (molecular and cellular), the cellular membrane is changed: emboly, perforation, and enlargement of cellular wall. The perforation of the cellular wall of a microorganism by nanoparticles leads to the discharge of the intracellular matrix [19, 21, 22].

The antibacterial activity of metal nanoparticles and their oxides is determined by their small size and extended surface. This provides their close contact with the cellular membrane of a microorganism [20, 23]. The size of nanoparticles plays the key role in their interaction with cellular enzymes, membrane proteins, and other components of the bacterial cell (e.g., with tryptophanase of *E. coli* according to the data of N.S. Wigginton). Such interaction leads to the damage of enzyme configuration [24]. The research of A.A. Rahmetova (2011) shows that cuprum nanoparticles with different dispersity and phase compositions have different antibacterial activities [23]. Moreover, a lot of research shows a direct correlation between metal nanoparticles and their antibacterial activity [25–27]. Smaller nanoparticles have more developed surface areas. This leads to a more effective interaction between it and the bacterial cell and, as a result, a more pronounced antibacterial effect.

INFLUENCE OF SILVER NANOPARTICELS ON PROKARYOTIC CELLS

Metal nanoparticles have strong biological activity, including bacteriostatic and bactericide. A number of works describe the antibacterial action of silver nanoparticles, including action against polyantibiotic-resistant strains [28–39]. It is noted that ultrafine silver has a stronger antibacterial effect than its ionic form [31].

A number of authors established that ultrafine silver can extricate ions. This determines the main mechanism of its antibacterial activity [40–44]. Extricated silver ions inhibited the activity of respiratory enzymes. This leads to the activation of free oxygen and damage of bacterial cell [45].

Silver nanoparticles can absorb to the cellular wall of a microorganism. This leads to its perforation [14].

Silver nanoparticles bind to phosphorus- and sulpha-containing compounds, such as proteins and nucleic acids, on the surface of a bacterial membrane and also inside of a cell [46]. Silver ions produced by nanoparticles interact with phosphorous-containing fragments of DNA. This leads to the inactivation of replication. When silver ions interact with sulfur-containing proteins, the inhibition of their function happens [47, 48].

The manifestation rate of the antibacterial action of silver nanoparticles depends on their size and shape [46, 49]. Studies show that silver triangle nanoparticles are more effective as bactericide agents against *E. coli* than nanoparticles with spherical and rod shapes. The reasons for this effect are not at all clear [31].

INFLUENCE OF CUPRUM NANOPARTICLES ON PROCARYOIC CELLS

The antibacterial activity of cuprum nanoparticles is now a well-known fact [50–52]. Studies of N. Cioffi et al. (2005) demonstrated the bacteriostatic and antimycotic action of ultrafine metal particles [53]. J. Ramyadevi, et. al. (2012) researched the bactericide action of cuprum nanoparticles against *Micrococcus luteus, S. aureus, E. coli, Klebsiella pneumonia, P. aeruginosa, Aspergillus flavus, A. niger*, and *Candida albicans* [54]. According to the data of these authors, the antibactericide action of cuprum nanoparticles was more expressed than their fungicide activity.

The antibacterial action of cuprum nanoparticles is associated with the influence of silver nanoparticles by their activity [55]. K. Yoon, et. al. (2007) researched the influence of cuprum and silver nanoparticles on standard strains of *Bacillus subtilis* and *E. coli*. They determined that cuprum nanoparticles with a dispercity of 100 nm had high activity against *B. subtilis*. At the same time, silver nanoparticles with a dispercity of 40 nm showed low activity against strains of *E. coli* [56].

The mechanism of antibacterial activity of cuprum nanoparticles is an open issue. It is evident that the start of the interaction between metal nanoparticles and the bacterial cell is the electrostatical interaction between the negative-charged surface of the microorganism and positive-charged metal nanoparticles. Research by D.G. Deryabin et al. (2013) of the zeta-potential of cells of the sensor K12 TG1 *E. coli* strain shows positive values of ζ-potential results for bacterial cells and negative ones for cuprum nanoparticles. When cuprum nanoparticles interact with a suspension of microorganisms, a drift of values to a positive result is obtained. This confirmed the theory of resultant electrostatic attraction. Electron microscopic studies indicate the advantage of this theory. They show contact between cuprum nanoparticles with the surface of bacterial cell [57, 58]. Due to this interaction, peptidoglycane is hydrolyzed; an increase in osmotic pressure leads to the explosion of murein sacculus and the extraction of cytoplasmatic components and fragments of cell wall.

Only one mechanism of the antibacterial effect of cuprum nanoparticles associated with the damage of the barrier function of the cellular membrane of an microorganism is obtained in the study of V.S. Lebedev et al. (2002). It is determined that processing bacterial cell by cuprum nanoparticles leads to the escape of K^+, which determines the summation of redox processes in the premembrane area [59].

Nanostructural metal can be the reason for the extraction of natrium, calcium, phosphorus, and kalium. It leads to the destabilization of membrane and the loss of cellular components [19]. Calcium plays an important role in the cellular metabolism and saving of lipopolyssacharide assembly on the surface of gram-negative bacteria [60].

Research by D.G. Deryabin et al. (2013) on the study of antibacterial activity of cuprum nanoparticles on luminescent strains of *E. coli* (*E. coli K12MG1655 pSoxS::lux, ketG::lux, recA::lux*) determined the mechanism of antibacterial action of nanoparticles due to oxidative stress. This mechanism is caused by the transfer of electrons to molecular oxygen among cuprum nanoparticles fixed in the membrane of a bacterial cell. The result of it is damage to the DNA molecule by reactive oxygen intermediates [57].

It is determined that the antibacterial activity of cuprum nanoparticles depends on numerous factors such as temperature, aeration, pH, and the concentration of nanoparticles and bacterial cells. It was shown that high temperature and aeration, as well as low pH and agglomeration, amplify the antibacterial activity of cuprum nanoparticles. Low agglomeration provides a large area of surface of metal nanoparticles for interaction with bacterial membrane [61].

Data on the antibacterial activity of cuprum nanoparticles allowed the United States Committee for Environmental Conservation to confirm their registration as an antimicrobial agent against malignant bacteria [62].

INFLUENCE OF TITANIUM OXIDE NANOPARTICLES ON PROCARYOTIC CELLS

Titanium oxide nanoparticles (TiO_2) have photocatalytic activity. The photocatalytic activity of TiO_2 nanoparticles is manifested in the fact that these particles can catch electrons of closer molecules under exposure to light. If nanoparticles are in water solution, this process leads to the formation of reactive oxygen intermediates, especially hydroxyl–radical [63]. Lipopolyssacharides, peptidoglycanes, and lipids of the cell membrane of microorganisms are oxidized under exposure to formed HO and O_{2-} radicals [64–66]. This is the cause of antiseptic features of TiO_2 nanoparticles [63, 67]. Moreover, it is showed that TiO_2 is genotoxic, because it interrupts the effects of DNA chains in cells under exposure to light [68, 69].

Research by G.B. Zavilgelsky et al. (2011) showed that hydric dioxide is formed in the cells of *E. coli* under the activity of titanium dioxide nanoparticles irradiated by UV-A. Hydric dioxide leads on oxidative stress and the death of the microorganism [70].

In a number of studies the antibacterial activity of titanium dioxide nanoparticles under exposure to UV light is shown. It is also shown that an increase in concentration of TiO_2 nanoparticles and intensity of UV radiation leads to an increase in its antibacterial activity. The highest antibacterial effect was observed while the cell wall of the microorganisms contacted TiO_2 nanoparticles, because of their absorption on the surface of the bacterial cell [71–76].

The antibacterial activity of titanium dioxide nanoparticles against *P. fluorescens* was studied; it was shown to dependend on their bactericide action on dispersity [77].

INFLUENCE OF NICKEL NANOPARTICLES ON MICROORGANISMS

Nickel nanoparticles have electroconductive and magnet characteristics, as well as a unique ability to keep his-tagged proteins [78, 79]. The ability of aggregates of nickel nanoparticles to associate with fragments of single-stand DNA (ssDNA) with the formation of stable complexes was shown [80].

The antibacterial action of nickel nanoparticles is not clear at all. There are isolated publications on the influence of this metal on particular members of microflora [53, 56, 81]. Thus, K. Yoon et al. (2007) researched the antimicrobial action of nickel and silver nanoparticles on standard strains of *E. coli* and *B. subtilis* in which nickel nanoparticles showed high antimicrobial activity [56].

H. Kumar et al. (2010) determined that nickel nanoparticles have a bactericidal effect in very low concentrations on standard strains of *E. coli, Lactobacillus spp., S. aureus, P. aeruginosa,* and *B. subtiles*. The character of antimicrobial activity was determined as oligodynamic [81].

According to research on animals, the toxicity of metal nanoparticles of ultradisperse powders of nickel have is less than the toxicity of silver nanoparticles [82].

CONCLUSIONS

Nowadays, one actual issue of medicine is the spread of polyresistant strains of microorganisms. Surely, the search for new antibacterial drugs against resistant strains of microorganisms is of theoretical and practical interest now.

The specific features of metals in ultrafine conditions open up wide possibilities for the creation of new effective materials and use in biology and medicine.

Metal nanopowders have strong biological activity, including bacteriostatic and bactericidal. Many authors have shown the bacteriostatic and bactericidal action of metal nanoparticles. Most studies are about the antibacterial activity of metal nanoparticles and their oxides, including those which are against resistant strains of microorganisms [28, 29, 31]. However, data on the mechanism of the antimicrobial action of metal nanoparticles need to be researched in future.

For the purpose of this review, there were no observed risk factors in medical use: issues of toxicity of metal nanoparticles, exposure levels for use of metal nanoparticles and their oxides, or risks of their accumulation in target organs.

A complex analysis of antibacterial action and risk factors of metal nanoparticles and their oxides offers the opportunity to detect more perspective drugs for clinical use against puoinglammatory suquela and other pathologies.

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