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Comparative Effects of Ionic and Nanoparticulate Silver on Nematodes *C. elegans* and Mice

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Abstract

The increasing use of silver nanoparticles (SNPs) in various fields of human activity concerns about their potential toxicity, particularly for invertebrates that absorb substances through their body surface and for terrestrial mammals. This study focuses on the interference of abiogenic silver with copper metabolism. This is due to the fact that Ag^{1+} and Cu^{1+} are isoelectronic, silver ions can be recognized by copper transporters and erroneously incorporated into essential cuproenzymes, thereby impairing their function. We conducted a comparative analysis of the biological effects of ionic silver (from $AgNO_3$) and nanoparticulate silver (30–40 nm spherical SNPs) on both wild-type *Caenorhabditis elegans* and a mutant strain with impaired copper excretion, as well as on the copper status in the serum of laboratory mice. The results revealed that SNPs exert greater toxicity in nematodes, particularly in those with disrupted copper homeostasis, whereas ionic silver posed a higher potential risk to mice. The findings highlight the need for cautious evaluation of SNPs in biomedical applications.

Keywords: Silver nanoparticles; Ionic silver; Copper status, Ceruloplasmin

1. INTRODUCTION

Silver nanoparticles (SNPs) are widely used in medicine, agriculture, food and textile industries due to their unique antimicrobial properties. It has been shown that the antibacterial properties of SNPs are due to their ability to enter the cell, causing the formation of reactive oxygen species, which are responsible for developing the genotoxic effect [1]. The effect of SNPs on bacteria is considered a nanospecific toxic effect. This explains the significant dependence of the antibacterial properties of SNPs on their linear size and shape [2,3]. At the same time, the SNP lethal dose (LD50) for cultured mammalian cells is at least 2 orders of magnitude higher than that of bacteria [4]. Moreover, they are generally considered low-toxic for mammals. However, SNPs even at low doses (2 mg per 1 kg of body weight), administered to mice intraperitoneally or intravenously, cause a decrease in copper status indicators, which include total copper concentration, ceruloplasmin (Cp, the main copper transporter through extracellular communication channels) oxidase activity, and Cp-associated copper concentration [5]. The effect is explained by the fact that the Ag(I) ion has a valence electron shell identical to the Cu(I) ion and a close atomic radius, which allows the silver ion to bind to intracellular copper transporters and reach the sites of cuproenzyme formation [6]. If the copper coordination centers include cysteine or methionine residues, Ag(I) can replace copper in these centers leading to a loss of enzymatic activity. It is also necessary that the specific cuproenzyme Cu-chaperone can bind silver ion. These conditions are combined in multicopper oxidases of such remote phylogenetic groups as bacterial

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and plant laccases and vertebrate Cp [7]. It seems that the SNPs effect on mammals is not the result of the action of the nanoparticles themselves but is primarily due to the release of Ag(I) ions through dissolution (ionic toxic effect). Probably, therefore, it significantly less depends on the shape and size of the particles [8,9]. Comparative studies devoted to the effect of ionic silver and nanoparticulate silver on copper metabolism in mammals have not been carried out. The results of such studies could provide valuable information on the dynamics of the influence of silver ions of different nature on copper metabolism, which should be taken into account in influenza infection therapy [10–12] and has already been used during the COVID-19 pandemic [13,14]. They also contribute to better understanding of the mechanisms that ensure the homeostasis of copper, participate in the regulation of signaling pathways, apoptosis, the activity of transcription factors and other processes [15]. In addition, disruption of copper homeostasis leads to the development of copper-associated diseases, which include such widespread diseases as the titular ones (Wilson, Menkes, Alzheimer, and Parkinson), cardiovascular and oncological diseases, as well as osteoporosis, metabolic syndrome, etc. [16].

Of particular interest is a comparative study of the effect of ionic and nanoparticulate silver on nematodes because *C. elegans* is intensively used as a model organism for studying copper-associated diseases [17]. The value of this model is ensured by the fact that in *C. elegans*, the copper homeostasis system is simpler than that of mammals. Nevertheless, it possesses major structural and functional orthologs of human copper-regulatory proteins [18]. The development of approaches to the treatment of these diseases is associated with the use of copper chelators [19], and silver can be considered as an agent that reduces bioavailable copper [6]. Additionally, nematodes are used as test organisms in ecotoxicity studies. Since SNPs, unlike $AgNO_3$, may have nanospecific toxic effects, they must be identified.

To study the above issues, we conducted a comparative study of the effects of ionic and nanoparticulate silver on the physiological state of nematodes and copper status in mice.

2. MATERIALS AND METHODS

2.1. Biological objects

Escherichia coli cells of strain K802 (CGSC, New Haven, CT, USA) with the genotype F-, lacY1, λ-, 165 mcrA0, rfbC1, metB1, mcrB1, hsdR2 were grown aerobically in liquid or agar nutrient media based on bovine serum hydrolysate (Samson-Med, St. Petersburg, Russia) at 37 °C. *E. coli* cells were taken from an overnight liquid culture medium, washed with sterile water and diluted 1:20 in a solution containing $AgNO_3$ or SNP with the same silver concentration (specifically indicated in the legends). The cells were incubated at room temperature with constant shaking (OS-20 orbital shaker Biosan, Latvia). Control cell samples were incubated in water. After treatment, the cells were titrated using the 10-fold dilution method to assess cell survival through colony-forming ability on agar plates. Colonies were incubated at 37 °C and counted at different time intervals and expressed as colony-forming unit per mL (CFU).

The work also used *C. elegans* worms obtained from the Institute of Biosciences and Bioresources - Consiglio Nazionale delle Ricerche (IBBR-CNR, Naples, Italy). Two *C. elegans* strains were used: the wild type of Bristol N2 and the mutant strain cua-1 (knu781[H828Q]), further abbreviated as *cua-1*^{H828Q}. The mutant strain *cua-1*^{H828Q}, which has a corresponding amino acid substitution in the copper transporter protein CUA-1, corresponds to the most common mutation in the human *ATP7B* gene responsible for the development of copper imbalance in Wilson's disease [16]. The characteristics of the strain *cua-1*^{H828Q} have been described previously [17]. The nematodes were cultured at 20 °C on growth medium (NGM) in Petri dishes seeded with *E. coli* OP50 strain as a food source with different SNPs and $AgNO_3$ concentration (specifically indicated in the legends). The worms were transferred to a fresh dish every 5 days to avoid starvation.

The work was also carried out on 8–12 week-old female CBA mice weighing 18–22 g (Rappolovo nursery, Leningrad region, Russian Federation). The animals were kept in polycarbonate cages with wood sawdust at a controlled temperature (23–25 °C), with a 12:12 h light-dark cycle, 60% humidity, and a free access to food and water.

2.2. Silver nanoparticles

SNPs were prepared by reducing silver from $AgNO_3$ solution using hydrazine hydrate in micelles formed by potassium oleate. Their physicochemical properties were characterized previously [8]. According to the absorption spectra in the UV/visible range, transmission electron microscopy, laser diffractometry, X-ray diffractometry, and sedimentation velocity, SNPs had a spherical shape with a size ranging between 30–40 nm with polydispersity index 0.01. The sizes of the SNPs were controlled by changing the conditions of their synthesis. The aqueous suspension of SNPs contained only crystalline silver without detectable traces of silver ions. The SNPs preparations preserve the same properties even after one a year.

2.3. Lifespan study

Nematodes synchronized at the embryonic stage were cultured on Petri dishes with different concentrations of $AgNO_3$ or SNPs. After 4 days, sexually mature nematodes were transferred to fresh dishes containing the same con-

centrations of $AgNO_3$ or SNPs every 2 days until all individuals under the experiment died. During the transfers, individuals living in each experimental group were counted. Nematodes that died due to crawling out on the walls of the dish, hatching of larvae inside the maternal gonad, or rupture of the vulva were excluded from the experiment.

2.4. Dynamics of distribution of ionic and nanoparticulate silver in mice

In experiments of pulse chase type, mice were intraperitoneally injected with SNPs at a dose of 3 mg/kg body weight. Peripheral blood, liver, spleen, kidney, and lung samples were collected at different intervals, ranging from 5 min to 32 h. At least three animals were examined at each time point. Silver and copper concentration, Cp oxidase activity, and the relative content of immunoreactive Cp were also measured in blood serum. Silver concentration was measured in tissue samples. In experiments with repeated administrations of SNPs, mice were intraperitoneally injected with SNPs at a dose of 2 mg/kg body weight daily for 7 days. Peripheral blood, liver, spleen, kidney, and lung samples were collected from three mice. Serum and tissue samples were analyzed as described below.

2.5. Subcellular fractions of the liver

Subcellular fractions of the liver were isolated from 150 mg of the liver that were homogenized three times for 30 sec using T 10 basic ULTRA-TURRAX disintegrator (IKA, Germany) at a 1:6 ratio in 0.25 M sucrose prepared in homogenization buffer (HB) containing 10 mM tris-HCl buffer, 120 mM KCl, 5 mM $MgCl_2$, 5 mM dithiothreitol, and 0.5 μg/ml cocktail of protease inhibitors. The homogenate was fractionated by the standard differential centrifugation method. Briefly, the homogenate was centrifuged (Allegra X-30R centrifuge, Beckman Coulter, USA) for 10 min at 1000g. The sediment was used as a source of nuclei. Mitochondria (12000g pellet, 20 min) and the Golgi complex with endoplasmic reticulum (29000g pellet, 1 h) were isolated from the supernatant by successive sedimentations. The supernatant after the last centrifugation was considered cytosol.

2.6. Determination of the Cp immunoreactive polypeptides content by immunoblotting (WB)

WB analysis was carried out as described earlier [20]. Blood serum proteins were separated by polyacrylamide gel electrophoresis (PAGE) under denaturing conditions using a Mini-PROTEAN Tetra system (Bio-Rad, USA). The protein content in the samples was 30 μg per lane. Proteins were transferred to a nitrocellulose membrane (pore size 0.45 μm, Bio-Rad, USA) using the "wet" transfer method. Transfer was carried out in tris-glycine buffer with 20% ethanol at a constant current of 350 mA for 1 hour, the quality of the transfer was controlled by staining the membrane with Ponceau S solution. The intensity of zones with the same molecular weight, stained for total protein with Ponceau S, was also used as a reference. After the transfer, the membrane was blocked for an hour with a 5% solution of skim milk prepared in PBST (PBS, 0.1% Tween-20). The membrane was then incubated overnight at 4 °C with the appropriate primary antibodies specific to the analyzed protein (Abcam, UK). After the incubation, the membrane was washed in PBST 5 times for 5 minutes, after which secondary antibodies conjugated with horseradish peroxidase were added at a concentration of 1:2000 and incubated for an hour. Subsequently, the membrane was washed in PBST according to the same scheme. Chemiluminescent detection was performed using the Clarity™ Western ECL substrate (Bio-Rad, USA) and the ChemiDoc Touch Imaging System gel-documenting system (Bio-Rad, USA)

2.7. Gel-filtration chromatography

Blood serum samples (2 mL) were fractioned using gel-filtration on a Sephadex G75 Superfine column (10–40 μm; 1.6×40 cm) in phosphate saline buffer, pH 7.4 (Bio-Rad, USA). The void volume of the column was estimated using blue dextran. Fractions (~1.5 mL per fraction) were collected and specified by A280.

2.8. Oxidase activity of Cp

Oxidase activity of Cp was measured by direct gel staining using the abiogenic substrate *o*-dianisidine: serum samples (2 μl) and plasma membranes (180 μg total protein) were separated electrophoretically in 8% PAAG under non-denaturing conditions. Gels were stained with *o*-dianisidine solution (Thermo Scientific, USA) to detect the oxidase activity of Cp and its GPI-linked form [21]. Stained electrophoretic gels and membranes with visualized antigen bands, obtained by WB (see 2.6), were analyzed using ImageJ software (NIH, USA) and expressed as % to control. The data are presented as a column chart.

2.9. The concentration of total protein

The concentration of total protein was determined using the Bradford colorimetric method. The reagent was prepared according to the standard protocol: 100 mg of Coomassie G-250 was dissolved in 50 mL of alcohol, 100 mL of orthophosphoric acid was added, and the solution was brought to 1 L with water. Bovine serum albumin preparations were used to construct the standard curve. Samples with the reagent were mixed in a ratio of 1:30

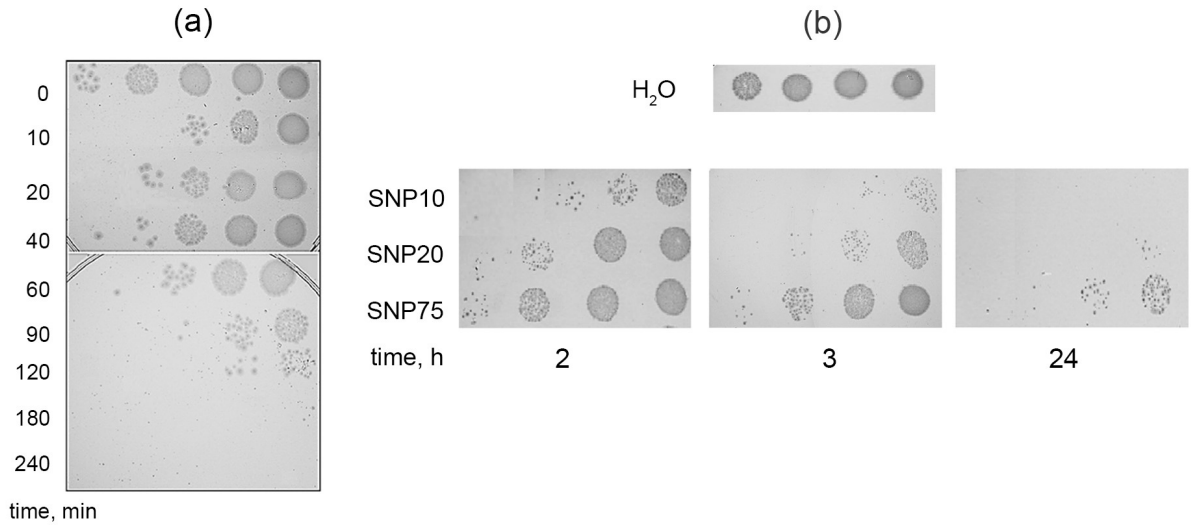

Fig. 1. Inhibitory effect of $AgNO_3$ and SNPs on the growth rate of *E. coli.* (a) Time-dependent sensitivity of *E. coli* cells to $AgNO_3$ ([Ag] is 3.5 μM). (b) Dependence of the colony-forming ability of *E. coli* on the incubation time and the SNP sizes. SNP silver concentration was 20 μM. 10-fold dilutions decreased from right to left.

in a serological plate, and absorption was measured at a wavelength of 585 nm using a CLARIOstar plate spectrophotometer (BMG LABTECH, Germany).

2.10. Copper and silver concentrations

Copper and silver concentrations were determined by atomic absorption spectrometry (AAS) with electrothermal atomization and Zeeman correction of non-selective absorption on a ZEEnit 650 P spectrophotometer manufactured by Analytik Jena (Germany). The samples were weighed and dissolved in nitric acid.

2.11. Statistical processing

Statistical processing was performed using one-way ANOVA with Tukey's post hoc test or a Kruskal-Wallis test with Dunn's post hoc test for multiple comparisons. More specifically, the method of statistical processing is indicated in the legends. The difference was considered statistically significant at a *p*-value less than 0.05. Survival curves were compared using the log-rank test (Mantel-Cox test). The difference was considered statistically significant when the *p*-value was less than 0.01.

3. RESULTS AND DISCUSSION

3.1. Comparison of the effect of ionic and nanoparticulate silver on the growth of *E. coli* cells

The results presented in Fig. 1a demonstrate that the presence of $AgNO_3$ in the culture medium at a concentration of 3.5 μM causes complete inhibition of bacterial growth after 2 hours of incubation. Nanoparticulate silver even at the concentration 20 μM does not cause complete inhibition of bacterial growth even after 3 hours (Fig. 1b). It is seen clearly that the inhibitory effect of SNPs depends on their size: the smaller the particle size, the higher their toxicity (Fig. 1b). Thus, SNPs with a diameter of 75 nm, i.e., the diameter almost reaches the size when they can no longer be classified as nanoparticles, do not completely inhibit the growth of *E. coli* even after 24 hours of treatment (Fig. 1b).

The data show that Gram-negative bacteria *E. coli* are more sensitive to ionic silver. These results are completely consistent with the data obtained with commercial SNPs [22]. However, its sensitivity to 10-nanometer particles is only one order of magnitude lower than to ionic silver. Therefore, it can be concluded that the antibacterial effect of SNPs is a sum of the action of silver dissociating from the surface of the nanoparticles (oxidative stress and genotoxic effect) and the ability of nanoparticles to overcome the bacterial outer membrane, which is limited by the size of the SNPs.

3.2. Effect of the ionic and nanoparticulate silver on the *C. elegans* lifespan of the wild type and strain with copper imbalance

The lifespan of the wild-type nematodes was approximately the same and corresponded to the control when treated with both ionic and nanoparticulate silver (Figs. 2a and 2b).

However, when treated with 9.0 μM $AgNO_3$, a 50% reduction in lifespan occurred on day 11 *versus* 16 days without treatment. Whereas, when treated with the same concentration of SNPs, 50% of the worms died by day 17.

Since wild-type nematodes exhibit resistance to silver, we used the *C. elegans* strain carrying the *cua-1*^{H828Q}

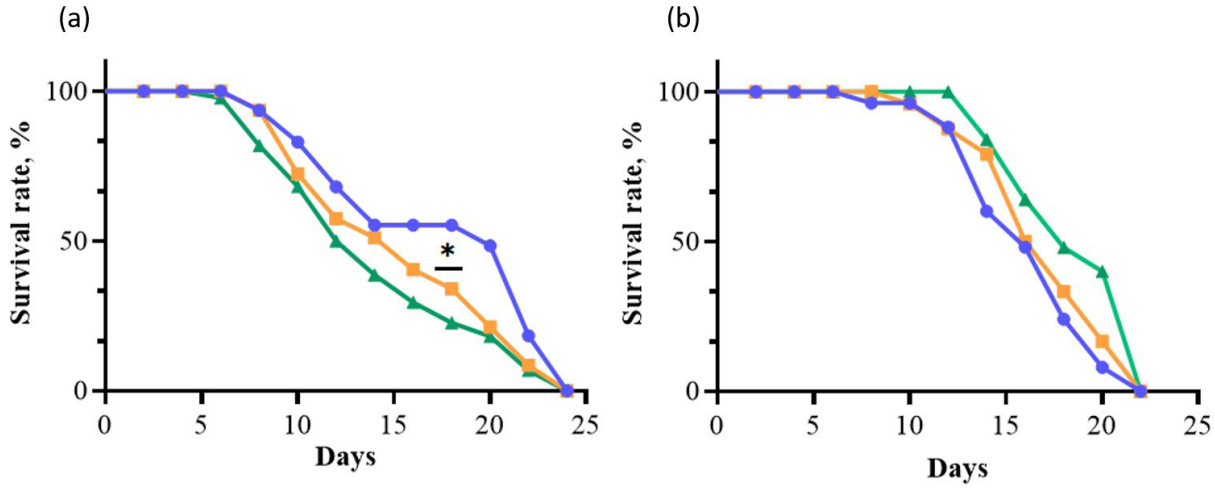

Fig. 2. Effect of $AgNO_3$ (a) and SNPs (b) on the survivability of *C. elegans* wild type. Abbreviation: blue – control; orange – 4.5 μM $AgNO_3$ or SNPs; green – 9.0 μM $AgNO_3$ or SNPs. * *p*-value < 0.01, Mantel-Cox test.

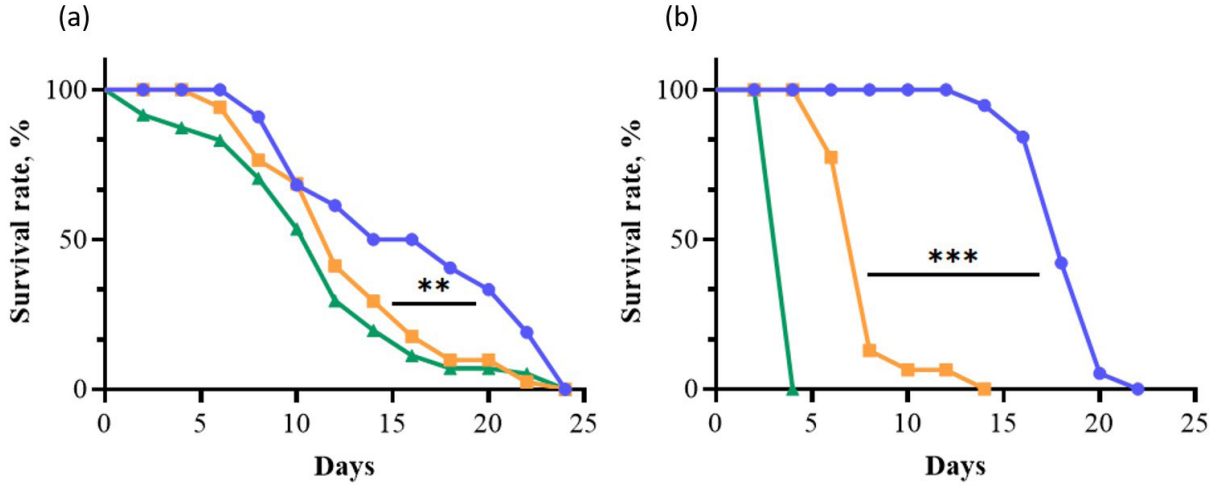

Fig. 3. Effect of $AgNO_3$ (a) and SNPs (b) on the survivability of *C. elegans* with copper imbalance. Abbreviation: blue – control; orange – 4.5 μM $AgNO_3$ and SNPs; green – 9.0 μM $AgNO_3$ and SNPs. ** *p*-value < 0.001, *** *p*-value < 0.0001 Mantel-Cox test.

substitution in the CUA-1 protein. Because the *cua-1*^{H828Q} strain is characterized by impaired copper and silver secretion [17], it is suitable for studying the effects of ionic and nanoparticulate silver. The results are shown in Fig. 3. They show that ionic silver, regardless of concentration, does not affect the lifespan of *cua-1*^{H828Q} nematodes (Fig. 3a). In contrast, nanoparticulate silver dose-dependently reduces the lifespan of this nematode strain by ~3- and ~6-fold when treated with 4.5 and 9.0 μM SNPs, respectively (Fig. 3b). The data clearly demonstrate that nematodes with impaired copper/silver excretion are highly sensitive to nanoparticulate silver. At the same time, SNPs with a diameter twice as large (approximately 60 nm) are less toxic than silver nitrate [23]. Therefore, conclusions about the comparative toxicity of SNPs and silver nitrate are valid only for SNPs of a specific size. This is likely due to similar mechanisms of action shared by both silver-based materials [23,24].

3.3. Distribution of silver in the body of mice

Unlike bacteria and invertebrates, which absorb substances from the environment through the body surface, silver can only be injected or administered orally to mammals. In mammals, silver concentration capable of causing a registered toxic effect is close to 50–100 mg per 1 kg of body weight. It is virtually impossible to achieve such concentrations of silver in the terrestrial environment. In this work, we used silver's ability to reduce oxidase activity in blood serum as a criterion for the effect of silver on mammals. We have previously shown that the most effective method of treatment is intraperitoneal administration, with 2 mg/kg of body weight administered daily for 5 days being sufficient to reduce oxidase activity to almost zero [8]. It has been shown that SNPs are effective in suppressing influenza and SARS-2 infections and can also decrease the tumor growth rate [10–14,25]; however, for their medical use there is a lack of data on the pharmaco-

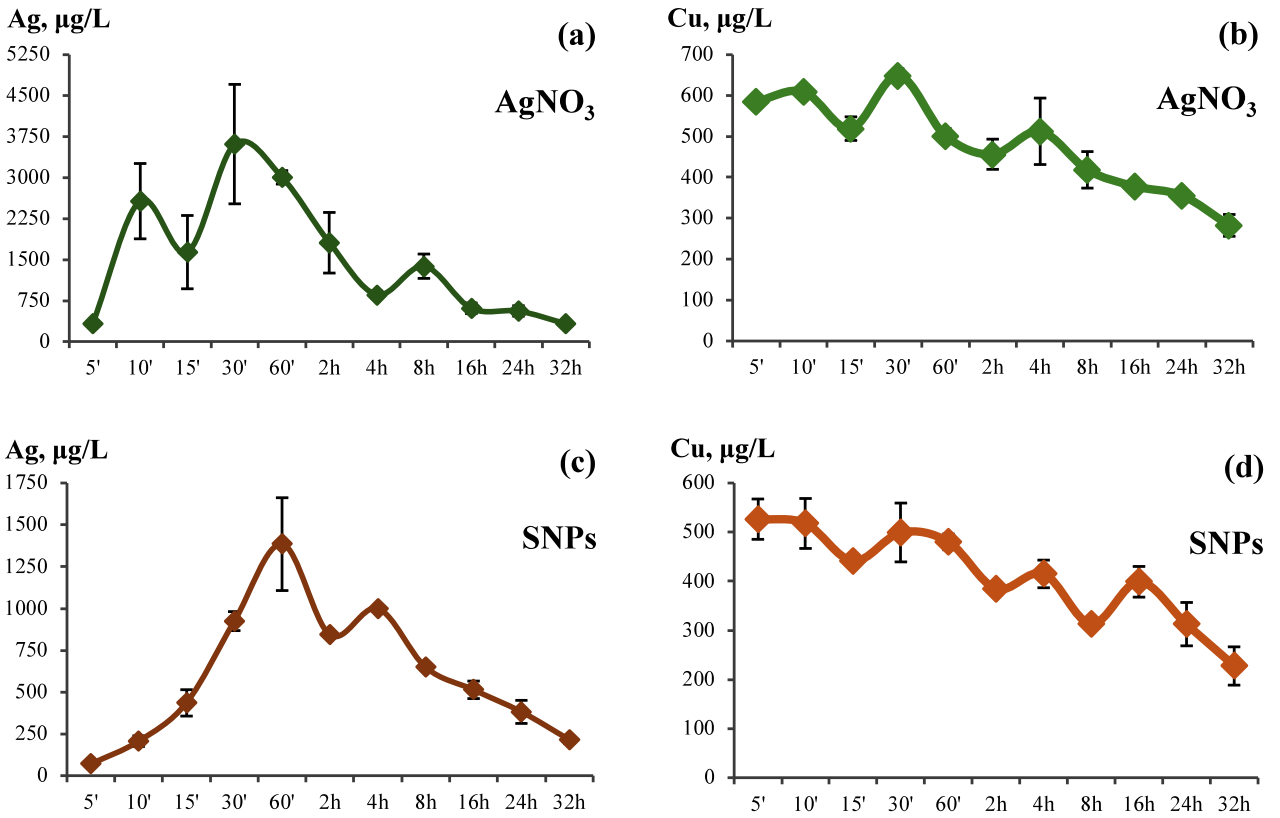

Fig. 4. Dynamics of the entry of ionic (a) and nanoparticulate silver (c) into the bloodstream and its effect on the copper content (b) and (d).

kinetics of ionic and nanoparticulate silver. The results of the pulse chase experiment show that $AgNO_3$, compared to SNPs, enters the blood faster (30 min *versus* 60 min, respectively; Figs. 4a and 4c). After reaching the maximum, the concentration of both silver types progressively decreases. Interestingly, at the same concentration of injected $AgNO_3$ and SNPs, the concentration of ionic silver in the blood serum is 2.5 times higher.

The copper concentration in these serum samples decreases in the same manner when treated with $AgNO_3$ and SNPs (Figs. 4b and 4d). In parallel with the increase in silver concentration and the decrease in copper concentration, the oxidase activity decreases by almost 5 times (Figs. 5a and 5b). At the same time, when mice are treated with ionic silver, a 50% decrease in oxidase activity occurs later than when mice are treated with silver nanoparticles (16 hours *versus* 8 hours, respectively). Interestingly, nanoparticulate silver reduces oxidase activity uniformly, while ionic silver reduces its impulse.

The decrease in oxidase activity occurs due to the substitution of copper by silver in the Cp molecule (Fig. 5c). At the same time, according to immunoblotting data, the concentration of the immunoreactive protein Cp does not change if the animals receive silver injections for 7 days and 7 days after their cancellation (Fig. 5d). In such experiments, the silver content increases, and copper decreases, and after the cancellation of injections, the copper status indexes are restored (Fig. 6).

Comparison of the dynamics of ionic and nanoparticulate silver distribution in the body of mice revealed two features. First, the concentration of ionic silver, compared to nanoparticulate silver, was an order of magnitude higher in the liver, but not in other organs considered (Figs. 7a and 7b). Second, with the $AgNO_3$ injection, starting from the 30th minute, the main part of the silver is found in the liver. Here, its concentration increases up to the 8th hour, then decreases. On the contrary, in mice treated with SNPs, the concentration of silver in the spleen exceeds that in the liver, both with a single administration (up to 24 hours) and in the following 7 days of daily injections (Fig. 7b). The concentration of silver in the liver, although lower than in the spleen, is close to it (Fig. 7b).

At all time intervals silver was detected in low concentrations in the kidneys and lungs. Rapid accumulation of nanoparticulate silver in the spleen may be related to the anatomical and physiological relationships between the spleen and liver. Thus, most of the silver entering the blood is transported to the liver through the portal vein system. Part of the blood from the portal vein through the splenic vein enters the spleen, which performs the function of capturing foreign substances, including particles, by phagocytic cells. This assumption is supported by data

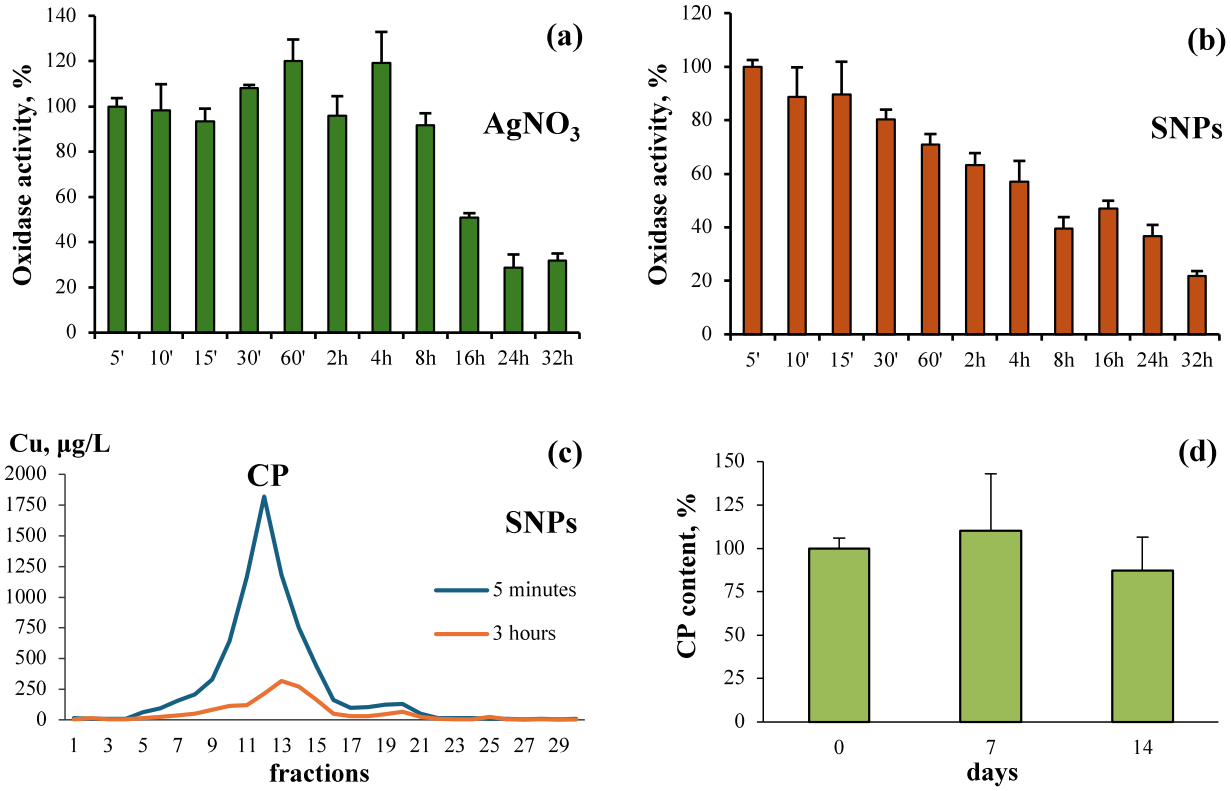

Fig. 5. Effect of intraperitoneal silver administration on oxidase activity in mouse serum. Time curve of oxidase activity decreases after a single administration of $AgNO_3$ (a) or SNPs (b). (c) Gel filtration of mouse serum 5 min (blue) and 3 h (orange) after SNPs administration. Abscissa – eluate fraction number; ordinate – copper concentration, µg/L. The Cp peak was identified by immunoblotting. (d) Concentration of immunoreactive Cp in the serum of mice: not treated with silver (day 0, 100%), after daily injections of SNPs for 7 days (day 7) and 7 days after cancelation of injections (day 14).

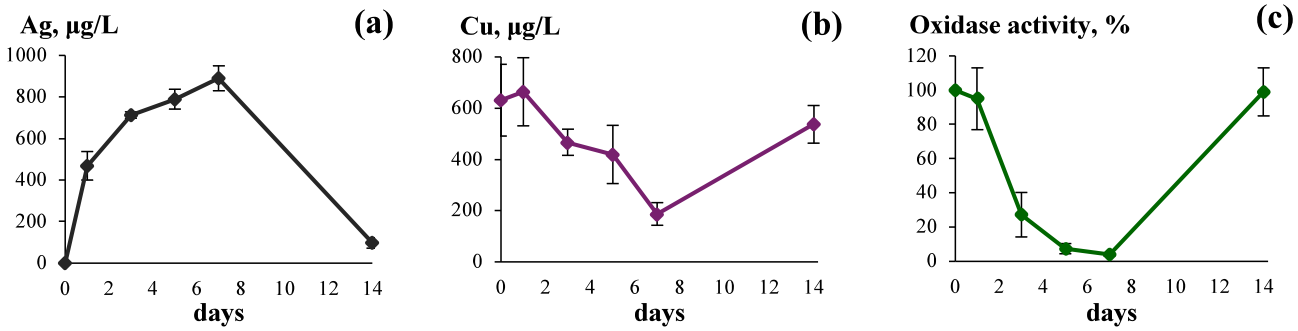

Fig. 6. Effect of silver injections and their withdrawal on blood levels of silver (a), copper (b), and oxidase activity (c).

demonstrating that in the spleen, the injected SNPs are localized in the cytoplasm of macrophages, in the marginal zone of the white pulp, and in the red pulp, sometimes in endothelial cells [26]. The removal of silver from organs begins 16 hours after injection, however, after 32 hours, its content in the liver and spleen remains high. The revealed difference between the ionic and nanoparticulate silver traffic in the mouse body possibly indicates that SNPs can be transported through the bloodstream.

The intracellular silver distribution was determined in organelles isolated from the liver of mice administrated with $AgNO_3$ or SNPs for 5 days. The results are shown in Fig. 8. They demonstrate that in cells, silver is delivered to all organelles, and it accumulates predominantly in the nucleus and mitochondria. The silver level does not depend on its source.

4. CONCLUSION

Despite the fact that the main bioactive agent of both $AgNO_3$ and SNPs are Ag^{1+} ions, one cannot ignore the fact that ionic and nanoparticulate silver can have different effects on organisms [27]. Summarizing the presented results, it can be concluded that the effect of $AgNO_3$ and

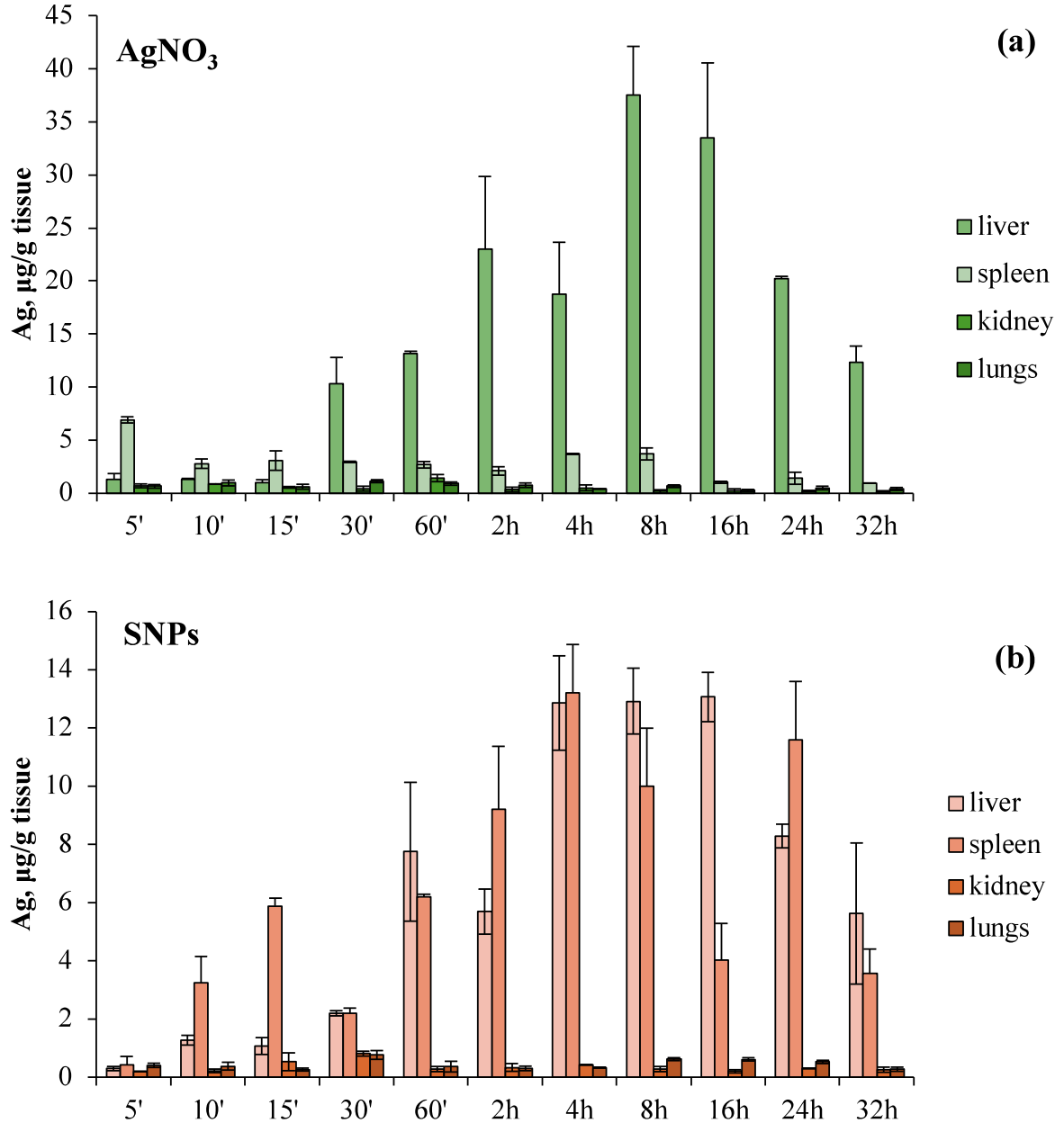

Fig. 7. The silver distribution in the body of mice depending on the source of silver: silver nitrate (a) and SNPs (b). Abscissa – time after a single administration of silver, ordinate – silver concentration, µg/g tissue. Each group consisted of three individuals.

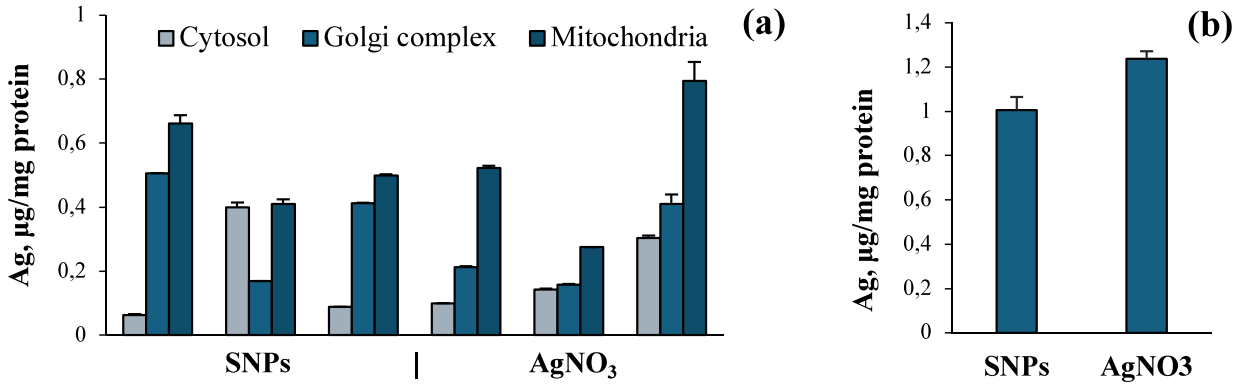

Fig. 8. Subcellular distribution of silver in the liver cells of mice administrated with $AgNO_3$ or SNPs for 5 days. (a) Silver concentration in the cytosol, Golgi complex, and mitochondria; data are shown for each of three mice per group, (b) silver concentration in nuclei, mean values for three mice ±SD are shown.

SNPs differs depending on the object of action. Thus, *E. coli* is more sensitive to ionic silver. However, nanoparticulate silver is highly toxic to nematodes with an impaired copper balance. In mammals, ionic and nanoparticulate silver do not differ in concentration and distribution in cellular compartments, as well as in the ability to interfere in copper status, possibly because Cp is a source of silver to non-hepatic cells. At the same time, the rate of absorption, entry into the liver and accumulation in organs is higher for ionic silver compared to nanoparticulate silver. Perhaps this is because ionic silver in a biological environment binds to small molecules (amino acids, monosaccharides, etc.), which ensures its rapid delivery in high concentrations to the liver. On the contrary, SNPs are partially captured by macrophages, which reduces their bioavailability, but, on the other hand, they are a reproducible source of silver ions dissociating from their surface. At the same time, they maintain stability, although lower, concentrations of bioavailable silver. The rate of inclusion of both types of silver in copper metabolism is limited by the rate of expression of genes whose protein products transport copper, ensuring its delivery to the sites of formation of cuproenzymes. However, the use of silver nitrate is complicated by the introduction of toxic anions $(NO_3)^{1-}$. Therefore, the criterion of SNPs can be recognized as preferable.

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Сравнение биологического действия ионного серебра и серебра в виде наночастиц на нематод *C. elegans* и мышей

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Аннотация. Широкое применение наночастиц серебра (НЧС) в различных сферах деятельности человека ставит проблему их токсичности как для беспозвоночных, способных поглощать вещества из окружающей среды поверхностью тела, так и для наземных млекопитающих. В представленной работе изучена способность абиогенного серебра вмешиваться в метаболизм меди. Известно, что Ag^{1+} и Cu^{1+} изоэлектронны, поэтому серебро способно распознаваться транспортерами меди и включаться в состав жизненно важных медь-содержащих ферментов, нарушая их активность. Сравнительное исследование влияния ионного серебра ($AgNO_3$) и серебра в виде наночастиц (сферические НЧС размером 30–40 нм) на нематоды *C. elegans* дикого типа и мутантный штамм с нарушенной экскрецией меди, а также на содержание меди в сыворотке крови лабораторных мышей показало, что НЧС более токсичны для нематод, особенно с нарушенным транспортом меди, а ионное серебро потенциально более опасно для мышей. На основании полученных данных обсуждаются перспективы использования НЧС в медицине.

Ключевые слова: наночастицы серебра; ионное серебро; статус меди; церулоплазмин