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Opinion

About therapeutic action of silver ions: A brief overview

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Abstract: A problem of sufficiency of the widespread worldview about the mechanism of silver ion's therapeutic action as its toxicity and destructivity for pathogens has been raised. Is such a therapeutic action always conjugated with direct destruction of the undesirable organisms such as bacteria, fungi, and cancer cells? Several works demonstrating a stimulating action of silver preparations on viability, proliferation of cells, behavioral and cognitive functions, and fertility of laboratory animals and on plants, as well as depletion of induced inflammation, have been considered. The observed effects can not be explained from the point of view of silver ion's toxicity. A mechanism, which is in eustress (positive stress) induction by silver ions in the exposed organism, is suggested. The mechanism is confirmed by experimental observations and centuries of successful experience in the use of silver preparations in medicine. However, for eustress realization and distress (negative stress) prevention, significant attention should be paid to the form of silver in the preparation, its dose, and the period of exposure as well as to the adaptive resources of the organism. The revealed mechanism should be taken into account at the development and testing of medicine as well as when it may be applied in clinical practice.

Keywords: silver; mechanism; therapeutics; eustress; distress

1. Introduction

Pure silver and its compounds have been applied by humanity in medicine since ancient times [1]. Nowadays silver nanoparticles, compounds of silver with sulfur, are actively used for wounds and burn treatment, pacemakers and implants are coated with silver to improve their biocompatibility. The problems of silver nanoparticle application in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases and multiple sclerosis treatments as well as cancer treatment are being actively studied [2–4].

Louis Pasteur's research in the 19th century on the pathogenicity of microorganisms formed the basis of the generally accepted worldview about the toxic effect of silver ions on pathogenic organisms, which remains today. Indeed, the most often used terms in scientific works concerning silver nanoparticles and silver ion effects characterize the destruction and killing of bacteria, fungi, and viruses [5–7]. The frequency and intensity of the use of terms such as "kill" and "destroy" in relation to living organisms, even pathogenic ones, is striking. A great number of scientific conferences of the 2010–2020s are devoted to Nanotoxicology and Nanosafety. One of the most discussed subjects at such events are problems of safe production, circulation, and utilization of silver nanoparticles.

Toxicity of silver preparations is frequently explained by induction of oxidative stress inside cells by silver ions, which leads to metabolism disturbance, genetic changes, apoptosis, and necrosis [8,9]. Thus, it is frequently considered that namely released silver ions interact with cellular organelles and biomacromolecules. The other mechanisms of silver preparation's toxicity are disruption of the plasma membrane integrity, lysis, and direct interaction of silver nanoparticles with cellular biomacromolecules [5,10].

It is clear that the principle of the action of silver preparations is seen by the scientific community, namely, in their toxicity and destructive, depleting action. How justified is this opinion? To what extent does it cover the available experimental baggage and centuries-old experience of using silver-containing preparations? Next, by analyzing scientific literature, we will try to understand this issue.

2. Stimulating effects at exposure to silver preparations

The main obstacle for the widely accepted worldview of the silver ion's therapeutic action such as, namely, its toxicity is in the stimulating, recovery effects observed at exposure to silver preparations. There are scientific works showing such stimulation effects of silver preparations at the cellular as well as at the general organism level. Let's consider some of them.

2.1. In vitro studies

The effects of exposure to different doses of silver nanoparticles and zinc oxide nanoparticles (10, 25, 50, 75 and 100 μg/mL) on human epithelial colorectal adenocarcinoma cells as an example of a cell line were investigated in [11]. A dose-dependent cytotoxic effect of zinc oxide nanoparticles and stimulation of cell viability at low doses of silver nanoparticles (10, 25, 50, 75 μg/mL) were observed. The authors pointed out that they observed hormesis [12], i.e., a stimulating effect, at silver nanoparticle exposure. Herewith, they found a significant number of oxidative stress markers at zinc oxide nanoparticle exposure and a lower amount of such markers at exposure to silver nanoparticles. The authors suggest that the increased viability of adenocarcinoma cells upon exposure to low doses of silver nanoparticles may be the result of general processes involved in the activation of adaptive responses necessary to protect cells from oxidative stress.

The influence of different concentrations of silver nanoparticles on human HepG2 cells was studied in [13]. Low doses (< 0.5 mg/L) of silver nanoparticles increased proliferation of the cells, and high doses (> 1.0 mg/L) of them induced significant cytotoxicity as well as anomalous morphology of cells such as contraction and deformation.

2.2. Animal models and clinical practice

In vivo studies where improvement and stimulation of organism functions at silver preparation exposure observed are rather interesting. An increase in locomotion and a decrease in the anxiety-phobic level in a stressful environment, as well as a violation of short-term habituation in rats after a 2-month administration of ~17 nm-sized silver nanoparticles, stabilized by beta-cyclodextrin, in the dose of 51 μg/kg bw were noted in [14]. 3 months after the withdrawal of nanosilver, behavioral functions and the ability for non-associative learning did not differ from the control. An increase in locomotion can be considered as a compensation for increased anxiety, which further led to a decrease in it. The effects of 1%, 10%, and 100% water solutions of silver nanoparticles synthesized with the use of green tea extract and a typical green synthesis method on the behavioral functions of mice with induced inflammation, as well as on the inflammation itself, were studied in [15]. A decrease in temperature hypersensitivity, edema, anxiety and an increase in locomotion were observed in mice exposed to silver nanoparticles. Dose-dependent anti-inflammatory effects were observed in some cases as well. Thus, exposure of mice to silver nanoparticles vanished the inflammation features and led to their recovery.

Our previous studies on the influence of silver nanoparticles [16] and silver citrate [17] on the behavioral and cognitive functions of laboratory mice are interesting within the consideration of stimulating effects. These studies are identical in experimental conditions and reproduce each other except for the exposition substances. C57BL/6 male mice since the age of 2 months were daily orally exposed to 50 µg of silver nanoparticles or silver citrate per day per animal for 30, 60, 120, and 180 days. On the cessation of the exposure periods, the mice were tested in behavioral tests such as the Open field, Elevated plus maze, and Light-dark box, as well as in the fear conditioning task, to test long-term contextual memory. All the tests were conducted with a 1-day break between them. Herewith, the exposure to silver preparations was continued during testing to prevent silver elimination processes.

At exposure to silver nanoparticles [16], the changes in behavioral and cognitive functions can be described by a 3-staged process: 1) Anxiety increases at an early stage, 2) exploration behavior increases at the background of enhanced anxiety, 3) long-term contextual memory impairment occurs at the background of the absence of other behavioral changes. The process can be interpreted as a distress characterized by an exhaustion phase [18], depletion of long-term memory at exposure to silver nanoparticles and can be schematically interpreted as **Figure 1** with all the phases ordered one by one, such as the anxiety phase (1), resistance phase (2), exhaustion phase (3).

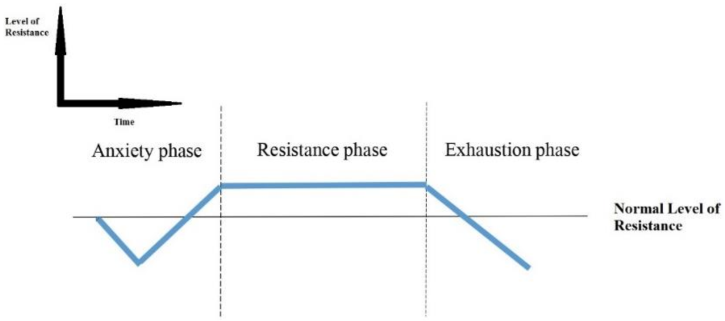

Figure 1. Schematically interpreted behavioral changes at silver nanoparticles' exposure from [16].

Special attention should be paid to the observed exploration behavior increase, i.e., stimulation of behavioral functions at the middle period of observation. The phenomenon can be regarded as the mice's adaptation to the toxin in the form of silver nanoparticles as compensation for increased anxiety, which, however, did not succeed—the impairment of long-term contextual memory was observed further. The attempt of mice to adapt to the toxin has a hormetic character.

A pronounced hormesis [12], such as stimulation of behavioral and cognitive functions of mice at silver citrate exposure, was observed in [17]. The changes in the behavioral and cognitive functions of mice in this case can be interpreted as a 3-staged process as well, such as: 1) anxiety increase at the early stage, 2) sensitivity increase, 3) tendency to improve long-term contextual memory at the background of decreased anxiety and locomotion increase. The behavior changes can be schematically interpreted as in **Figure 2**. Similarly to [14], the tendency to improve long-term memory and locomotion increase can be interpreted as a compensation for increased anxiety at the early stage. Herewith, the exhaustion stage was not found within the period of observation. It should be noted that the period of observation is a rather significant part (1/12) of a maximal life span of a mouse (36 months) [19]. The typical eustress, or, in other words, hormesis, which was expressed in the stimulation of long-term memory and locomotion in the mice exposed to silver citrate, was observed in the experiment.

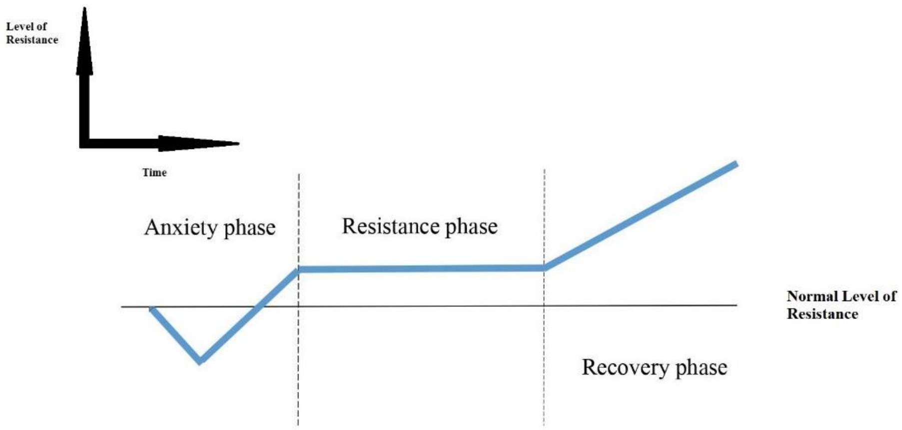

Figure 2. Schematically interpreted behavioral changes at silver citrate exposure from [17].

Therefore, comparing the experiments, we can conclude that silver citrate is more biocompatible than silver nanoparticles. The following question is principal. Why are silver nanoparticles more toxic compared to silver salt such as silver citrate, which is expressed in the oppression of the cognitive function of mice? This can be explained by the fact that silver nanoparticles are accumulated in tissues in the form of a depot of silver ions, gradually releasing the ions. It is likely that gradually released silver ions may cause chronic stress. Chronic stress, in its turn, may cause distress, decompensation, and oppression of the organism's functions, which was observed in the long-term contextual memory impairment. The influence of an anion should be taken into account as well [20]. Here the relative biocompatibility of the salt formed by lemon acid, such as silver citrate, could lower the salt toxicity. For example, equivalent impairments in cognitive function in rats were observed at silver nitrate [21], which is the salt of a stronger acid than lemon acid, as well as with silver nanoparticle exposure in the dose of 0.5 mg/kg bw during 28 days.

An increase in female mice fertility at silver nanoparticle exposure was observed in [22]. The experimental female mice were orally exposed to silver nanoparticles in the amount of 25 µg/mL since the week before mating and until the end of lactation. The experiment was repeated twice. A nearly twofold increase in the birth rate was shown in female mice exposed to silver nanoparticles compared to the controls. The survival rates of the offspring did not differ.

The stimulating regenerative effect of silver nanoparticles on epithelium growth is well known and is actively applied today in surgery for wound healing and burn treatment [23].

2.3. Agriculture

A stimulating effect of silver nanoparticles was observed in the experiments related to agriculture as well. For example, low doses of silver nanoparticles (0.3–10 mg L^{-1}) synthesized by a chemical technique using PVP and L-ascorbate stimulated the growth of birch plants. Under higher levels of nanoparticles (30–300 mg L^{-1}), the stimulating effect decreased. Concentrations over 300 mg of L^{-1} inhibited the growth of birch plants. High doses of silver nanoparticles synthesized using spruce needle extract (green synthesis technique) (3–300 mg L^{-1}) significantly stimulated growth of birch plants, while lower doses did not have such an effect [24]. The study [25] emphasized the potential of silver nanoparticles in agriculture is not only biocidal. It proved that silver nanoparticles with bigger size (30–60 nm)/negative charge, used in low concentration, can have a surprisingly stimulating effect on the positive characteristics of the rhizosphere microbiome, while silver nanoparticles with smaller size (10 nm) and positive charge enhanced harmful microbiota [25]. Also, it was found that silver nanoparticles in the dose of 2 mg L^{-1} at NaCl stress had a stimulating effect on some active compounds in garlic callus [26], which points to adaptation and activation of the defense system. It was demonstrated [27] that low doses of silver nanoparticles stimulated germination energy, seed viability, and root growth of watercress, Lepidium sativum L. Curled.

2.4. Generalization on stimulating effects

The reviewed stimulating effects on different organisms, with the emphasis on stimulating ones and with regard to doses and periods of exposure, are summarized in **Table 1**.

Table 1. Effects of silver preparations on different living organisms.

Type of preparation	Properties	Type of exposure	Type of organism	Positive effect
Silver nanoparticles [11]	~ 30 nm	10, 25, 50, 75 µg/mL, single	human epithelial colorectal adenocarcinoma cells	Increased viability, slightly increased number of oxidative stress markers
Silver nanoparticles [13]	7–10 nm, stabilized with polyethylenimine	< 0.5 mg/L, single	human HepG2 cells	increased proliferation
Silver nanoparticles [14]	~17 nm, stabilized with beta-cyclodextrin	51 µg/kg bw, 2-month administration, 3-month elimination	rats	Increase of locomotion as a compensation for previously increased anxiety

Table 1. (*Continued*).

Type of preparation	Properties	Type of exposure	Type of organism	Positive effect
Green-tea nanoparticles [15]	8 nm	0.3 mg/kg p.o. of 1%, 10% and 100% water solutions	BALB/c mice	Decrease in temperature hypersensitivity, edema, anxiety, increase of locomotion, dose-dependent anti-inflammatory effects
Silver nanoparticles [16]	34 ± 5 nm, stabilized with PVP	50 µg/day/animal for 30, 60, 120, 180 days, oral	C57BL/6 mice	Exploration behavior increases
Silver citrate [17]	Transparent water solution	50 µg/day/animal for 120 days, oral	C57BL/6 mice	Tendency to improve long-term contextual memory, locomotion increase, anxiety decrease
Silver nanoparticles [22]	8,7 ± 1,4 nm, stabilized with PVP	25 µg/mL/day since the week before mating and until the end of lactation, oral	SHK mice	increase in female mice fertility
Silver nanoparticles [23]	-	transdermal	human	epithelium growth, wound healing and burn treatment
Silver nanoparticles [24]	synthesized by chemical technique using PVP and L-ascorbate	0.3–10 mg L^{-1}	Birch plants	Stimulation of growth
Silver nanoparticles [24]	synthesized using spruce needle extract	3–300 mg L^{-1}	Birch plants	Stimulation of growth
Silver nanoparticles [25]	bigger size (30–60 nm) /negative charge	watering	rhizosphere microbiome	Positive effect
Silver nanoparticles [26]	-	2 mg L^{-1}	Garlic Callus	stimulating effect on some active compounds
Silver nanoparticles [27]	11.40 ± 3.96 nm	1,17, 2,34, 4,69 µg/mL for 1 h	Watercress Lepidium sativum L. Curled	Stimulation of root growth

Attempts to explain the stimulation effects from the point of view of the widely accepted concept of destructivity, toxicity of silver preparations for living organisms are unfounded and one-sided. If the substance is toxic for pathogens and cancer cells, it means that it can be toxic for beneficial microbes and for normal cells as well. For silver preparations, it is confirmed by various *in vitro* and *in vivo* studies [28,29]. There is an opinion in the scientific literature that silver preparations are more toxic for pathogens [30] and cancer cells [31] than for normal cells. Such a selectivity of silver ion's action is weakly explainable and requires careful selection of dosage, which is not consistent with historical facts indicating the successful use of silver preparations in quite wide ranges of doses and in different forms from metallic silver to nanoparticles.

A natural question arises: what mechanism really underlies the therapeutic action of silver preparations, and how is it related to the stimulating effects discussed above? It is obvious that direct destructive action of silver ions towards pathogens does not allow us to explain the mechanism of therapeutic action, taking into account the certain toxicity for the master's organisms and the observed stimulating effects. Such toxicity could lead to the oppression of the master's organism, while the directly opposite picture, such as stimulation at silver preparation's exposure, was observed in the above-considered works [11,13–16,22–27].

3. Stress as the mechanism of silver action towards living organisms

To better understand the stimulation effects of silver preparation's exposure [11,13–16,22–27] the studies [32–34], where cortisol level increased or decreased at such an exposure, should be discussed. In its turn, cortisol level change points to stress. Herewith, the stress can be eustress (positive stress) as well as distress (negative stress). They differ from each other by the character of the 3rd phase: it is adaptation for eustress and exhaustion for distress (**Figure 3**). The elevated earlier level of hormones falls to control values at the adaptation stage of eustress and lower than the control values for the exhaustion stage of distress [35]. Eustress is characterized by stimulation and activation of the organism's own resources, while distress is characterized by their exhaustion and depletion. Distress may later bring the organism to decompensation and chronic diseases as well as even death. The stress reaction is also confirmed by the anxiety level increase of the animals exposed to silver preparations, which was observed in [14,16,17] as well as in some other scientific works.

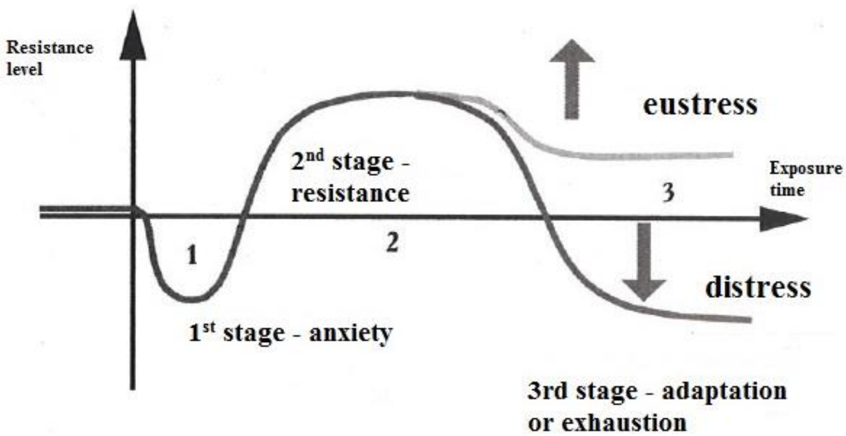

Figure 3. Scheme of eustress and distress stages. The first two stages, such as anxiety and resistance, are similar for both types of stress, while the last stages are different. The third stage is adaptation for eustress and exhaustion for distress.

It should be taken into account that silver is not an essential element for humans, animals, and plants [36,37]. Therefore, their organisms have to adapt to the unknown exogenous substance, while the adaptation to the changing environment always gives birth to stress. It easily explains the appearance of silver ions as a stressor.

Thus, we suggest below a new concept to explain the therapeutic action of silver preparations. As it was mentioned above, such preparations interact with organisms by means of the released silver ions. We believe that the mechanism of therapeutic action of silver ions is the induction of eustress by the ions in a living master's organism.

Let's consider the scheme of such a mechanism in the presence of bacterial, viral, or fungicidal infection, weakening the organism. At the stressor action, such as silver ions, Endocrine, Nervous, and Immune systems are activated first (**Figure 4**). Then the activated Immune system selectively neutralizes pathogens. The organism being eustressed recovers. Namely, the Immune system provides the selectivity of antiseptic action, and being activated by silver ions increases its efficiency.

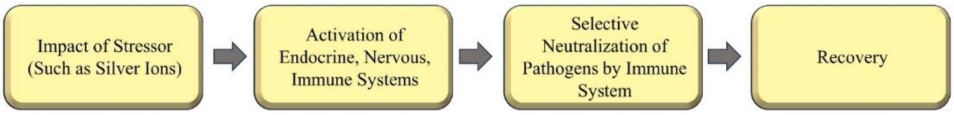

Figure 4. The scheme of the mechanism of pathogen neutralization in an organism.

In contrast to it, the traditional worldview about silver ion's therapeutic action is based on the direct destructive action of silver ions on pathogens. While we suggest that such an action is indirect and is accomplished via stimulation of the organism's own resources. The pathogens are effectively and selectively eliminated by the activated Immune system. The direct destructive action may lead to killing both pathogens, useful bacteria, and healthy cells, which is obviously undesirable. The direct mechanism is not supported by many centuries of successful application of silver in medicine as well.

Thus, we believe that the mechanism of therapeutic action of silver ions is not in the destruction of pathogens and cells by them. It is in stimulation, activation of the organism's own resources, which, in its turn, activates recovery processes. Stress at the general organism level can be triggered by cellular mechanisms such as oxidative stress as well as some other ones. Eustress or distress realization is determined by the dose, period of exposure, and own adaptive resources of the exposed organism. If stressor impact is lower than the organism's adaptive resources, then eustress is realized, but if it is higher than they are, it causes distress.

Eustress consideration as the mechanism of therapeutic action of silver ions easily explains the observed phenomena of cell viability and proliferation increase [11,13], improvement of behavioral and cognitive functions [14–17], fertility increase [22], skin regeneration [23], stimulation of plant growth [24,26,27] and improvement of soil quality [25] as well as depletion of induced inflammation [15] at silver preparation's influence.

It is likely that such a mechanism lies at the base of the experimentally observed improvements in neurodegenerative diseases and cancer treatment by silver nanoparticles. This is the stimulation and activation of the organism's own resources. It is similar to hardening, transformational psychological running [35] (jogging), and sauna. Herewith, the observed selectivity for master's organism survival increase can be explained from the point of view of the complexity of its structure, when some systems can replace the other ones when they the last ones are deactivated. Such stability is determined by its perfection. Complex systems possess higher adaptive resources and can better resist the effects of stressors than more simple ones.

Practical application

The revealed mechanism should be taken into account at the development and testing of medicine in future research. It is necessary to focus on the therapeutic action and not on the destruction of undesirable organisms and cells. Also, the ability of silver ions to induce eustress can be considered for application in clinical practice for the treatment of symptoms of neurological, mental, and some other diseases, which are known to be difficult to treat.

Nevertheless, the risks of chronic stress and distress over a long period and with high-dose exposure should not be forgotten. It is necessary to remember the words of the well-known Swiss medical doctor of the Renaissance, Paracelsus, such as “Solely the dose determines that a thing is not a poison”. Practically any substance in a significant dose can lead to destructive consequences.

4. Conclusions

We believe that the mechanism of therapeutic action of silver ions is not in killing or destroying undesirable organisms and cells by the ions but in eustress induction and indirect stimulation of the immune system, which, in its turn, selectively suppresses pathogens. The organism recovers at eustress conditions. Such a mechanism allows us to easily explain the observed stimulation phenomena at exposure to silver preparations and the successful application of silver in medicine within many centuries. The idea of the mechanism should be applied in future scientific studies and clinical practice. It is necessary to focus more on the therapeutic recovery effects of silver ions and less on their possible destructive effects, however, taking into account the risks of the latter.

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