About Therapeutic Action of Silver Ions: A Brief Overview

Antsiferova A.A.[1,2,*], Kashkarov P.K.[1,2,3]

1 National Research Center “Kurchatov Institute”, 1, Akademika Kurchatova sq., Moscow 123182, Russia
[2] Moscow Institute of Physics and Technologies, 9, Institutskii Lane, Moscow Region, Dolgoprudny 141700, Russia
[3] Department of Physics, Lomonosov Moscow State University, 1, GSP-1, Leninskiye Gory, 119991 Moscow, Russia
*aiyoga@yandex.ru

Abstract

A problem of sufficiency of the wide spread 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, cognitive functions and fertility of laboratory animals 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 a 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.

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, burns treatment, pacemakers and implants are coated with silver to improve their biocompatibility. The problems of silver nanoparticle’s application in neurodegenerative diseases such as Alzheimer’s, Parkinson’s diseases, 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 is still remain today. Indeed, the most often used terms in scientific works concerning silver nanoparticle’s and silver ion’s effects characterize the destruction and killing of bacteria, fungi and viruses [5-7]. The frequency and intensity of the use of the terms such as “kill” and “destroy” in relation to living organisms, even pathogenic ones, is striking. A great number of scientific conferences of 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]. 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 [10, 11].

It is clear that the principle of the action of silver preparations is seen by scientific community namely in their toxicity, 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.

1. Stimulating effects at exposure to silver preparations

There are scientific works showing stimulation effects of silver preparations at cellular as well as at the general organism level. Let's consider some of them. The effects of exposure to different doses of silver nanoparticles and zinc oxide nanoparticles on human epithelial colorectal adenocarcinoma cells as an example of a cell line were investigated in [12]. A dose-dependent cytotoxic effect of zinc oxide nanoparticles and stimulation of the cell viability at low doses of silver nanoparticles were observed. The authors pointed that they observed hormesis [13], i. e. stimulating effect, at silver nanoparticle's exposure. Herewith, they found a significant number of oxidative stress markers at zinc oxide nanoparticle's exposure and their lower amount 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.

Influence of different concentrations of silver nanoparticles on human HepG2 cells was studied in [14]. Low doses 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.

In vivo studies where improvement and stimulation of organism functions at silver preparation exposure were 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, were noted in [15]. 3 months after the withdrawal of nanosilver behavioral functions and the ability for non-associative learning did not differ from the control. Increase of locomotion can be considered as a compensation to increased anxiety, which further led to decrease of it. The effects 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 [16]. Decrease of temperature

hypersensitivity, edema, anxiety and increase of locomotion in exposed to silver nanoparticles mice were observed. Dose-dependent anti-inflammatory effects were observed in some cases as well. Thus, exposure of mice to silver nanoparticles vanished the inflammation features and lead to their recovery.

Our previous studies on the influence of silver nanoparticles [17] and silver citrate [18] on behavioral and cognitive functions of laboratory mice are interesting within the consideration of stimulating effects. These studies are identical by experimental conditions and reproduce each other except 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 Open Field, Elevated Plus Maze, Light-Dark Box as well as in Conditioning Fear Task to test long-term contextual memory. All the tests were conducted with 1-day break between them. Herewith, the exposure to silver preparations were continued during testing to prevent silver elimination processes.

At exposure to silver nanoparticles [17] the changes in behavioral and cognitive functions can be described by 3-staged process: 1) anxiety increase at early stage, 2) exploration behavior increase at the background of enhanced anxiety, 3) long-term contextual memory impairment at the background of absence of other behavioral changes. The process can be interpreted as a distress characterizing by exhaustion phase [19], depletion of long-term memory at exposure to silver nanoparticles.

A 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 adaptation to the toxin in the form of silver nanoparticles, as compensation to 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 [18]. The changes of behavioral and cognitive functions of mice in this case can be interpreted as 3-staged process as well such as: 1) anxiety increase at early stage, 2) sensitivity increase, 3) tendency to improve long-term contextual memory at the background of decreased anxiety and locomotion increase. Similarly to [15] the tendency to improve long-term memory and locomotion increase can be interpreted as a compensation to increased anxiety at early stage. Herewith, 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) from a maximal life span of a mice (36 months) [20]. The typical eustress or, in the 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.

Thus, 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 the 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 depot of silver ions gradually releasing the ions. It is likely that gradually releasing silver ions may cause chronic stress. Chronic stress, in its turn, may cause distress, decompensation and oppression of the organism functions, which was observed in the long-term contextual memory impairment. The influence of an anion should be taken into account as well [21]. 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 were observed at silver nitrate exposure, which is the salt of a stronger acid than the lemon acid, as well as silver nanoparticles [22].

An increase in female mice fertility at silver nanoparticle exposure was observed in [23]. 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 two-fold 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 the epithelium growth is well known and is actively applied today in surgery for wound healing and burn treatment [24].

Attempts to explain the stimulation effects from the point of view of the widely accepted concept of destructivity, toxicity of silver preparations for the living organisms are unfounded and one-sided. If the substance is toxic for pathogens, 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 [25-27]. There is an opinion in the scientific literature that silver preparations are more toxic for pathogens [28] and cancer cells [29] than for normal cells. Such a selectivity of silver ion’s action is weakly explainable and requires jewelry 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 to explain the mechanism of therapeutic action, taking into account the certain toxicity for the master’s organisms, and the observed stimulating effects. Such a 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 considered above works [13-17, 23, 24].

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

To better understand the stimulation effects at silver preparation’s exposure [13-17, 23, 24] the studies [30-32], 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 (Fig. 1). The elevated earlier level of hormones falls to control values at adaptation stage of eustress and lower than the control values for exhaustion stage for distess [33]. Eustress is characterized by stimulation, activation of organism's own resources, while distress is characterized by their exhaustion, depletion. The stress reaction is also confirmed by anxiety level increase of the animals exposed to silver preparations, which was observed in [15, 17, 18] as well in many others scientific works.

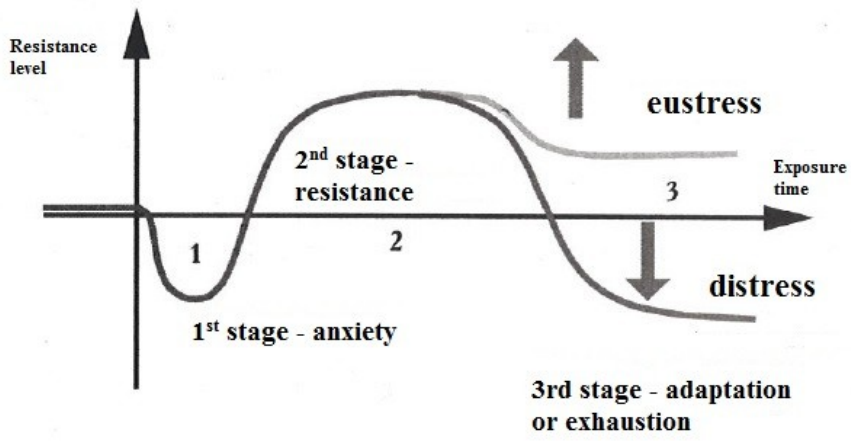

Figure 1. Scheme of eustress and distress stages. The first two stages such as anxiety and resistance are similar for both types of stress, while last stages are different. The third stage is adaptation for eustress and exhaustion for distress.

It should be taken into account that silver is not an essential element for humans, animals and plants [34, 35]. Therefore, their organisms have to adapt to the unknown exogenous substance, while the adaptation to the changing environment always gives a birth to stress. It easily explains the appearance of silver ions as a stressor.

Thus, we suggest below a new concept to explain 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 in induction of eustress by the ions in a living master's organism.

Let's consider scheme of such a mechanism at 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 (Fig. 2). Then activated Immune system selectively neutralizes pathogens. The organism being eustressed recovers. Namely, Immune system provides the selectivity of antiseptic action and being activated by silver ions increases its efficiency.

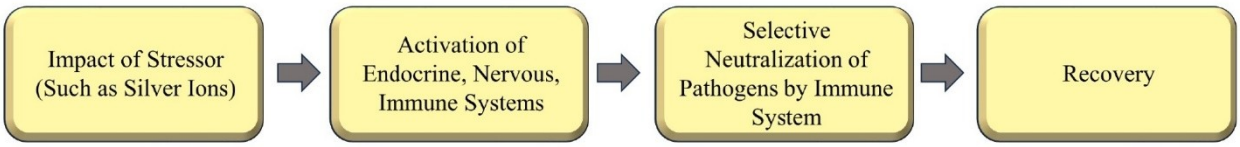

Figure .2. The scheme of the mechanism of pathogen neutralization in an organism.

Thus, we believe that the mechanism of therapeutic action of silver ions is not in the destruction of pathogens and cell by them. It is in stimulation, activation of 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 the 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 [13, 14], improvement of behavioral and cognitive functions [15-18], fertility increase [23], skin regeneration [24] as well as depletion of induced inflammation [16] at silver preparation's influence.

It is likely that such a mechanisms lies in the base of the experimentally observed improvements at neurodegenerative diseases and cancer treatment by silver nanoparticles. This is the stimulation, activation of organism's own resources. It is similar to hardening, transformational psychological running [33] (jogging), sauna. Herewith the observed selectivity for master's organism survival increase can be explained from the point of view of complexity of its structure, when some systems can replace the other ones when the they are deactivated. Such stability is determined by its perfection. Complex systems possesses higher adaptive resources and can better resist the effects of stressors than more simple ones.

The revealed mechanism should be taken into account at the development of new medicine. It is necessary to focus on the therapeutic action and not at the destruction of undesirable organisms and cells.

Nevertheless, the risks of chronic stress and distress at the long period and in high dose exposure should not be forgotten. It is necessary to remember the words of the well known Swiss medical doctor of 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.

Conclusions

We believe that the mechanism of therapeutic action of silver ions is not in killing, destruction of undesirable organisms and cells by the ions but in eustress induction and indirect stimulation of Immune system, which, in its turn, selectively suppresses pathogens. The organism recovers at eustress conditions. Such a mechanism allows to easily explain the observed stimulation phenomena at exposure to silver preparations and the successful application of silver in Medicine within many centuries.

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