Retraction Notice

Title of retracted article:	**Biochemical and Physiological Effect of Silver Bioaccumulation**
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Journal:	Open Journal of Pathology
Year:	2016
Volume:	6
Number:	1
Pages (from - to):	57 - 71
DOI (to PDF):	http://dx.doi.org/ojpathology.2016.61008
Paper ID at SCIRP:	1940170
Article page:	http://www.scirp.org/journal/PaperInformation.aspx?PaperID=63165
Retraction date:	2016-05-24

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Date initiative is launched: 2016-05-24

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Open Journal of Pathology, 2016, 6, 57-71
Published Online January 2016 in SciRes. http://www.scirp.org/journal/ojpathology
http://dx.doi.org/10.4236/ojpathology.2016.61008

Biochemical and Physiological Effect of Silver Bioaccumulation

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Received 22 October 2015; accepted 24 January 2016; published 28 January 2016

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Abstract

Recent studies have shown that silver is no longer restricted to just being found in soil and natural waters. The metal and its various forms are used in medicine as nanoparticles for various applications. After assimilating and reviewing a considerable volume of literature, it can be safely stated that silver displays different extents of bioaccumulation depending on the ecosystem involved. Aquatic ecosystems were revealed to be less prone to the toxic effects of the metal due to the buffering capacity of water and its dissolved contents. Evidence suggests that even though bioaccumulation is possible in terrestrial animals, biomagnification is not. Humans are more prone to bioaccumulation due to the use of silver nanoparticles in medicine. The toxic effects of silver are attributed to the formation of free silver (I) ions (Ag^+). Biochemical effects are brought about by interactions with proteins, deoxyribonucleic acid (DNA) and intracellular signalling pathways. Physiological effects are manifestations of biochemical effects in different regions of the body. Literature has shown that by means of physiological and biochemical effects, silver bioaccumulation gives rise to both benign and harmful disease, namely argyria, cardiovascular disease and respiratory disease.

Keywords

Silver, Nanoparticles, Bioaccumulation, Biochemistry, Physiology, Toxicity

1. Introduction

Planet Earth's environment has always had a rich variety of chemical elements. Heavy metals have been the subjects of hundreds of research programs in recent scientific history and development. Silver is one of these metals [1].

Metallic silver, as well as its compounds, has been used by the human race throughout history in a wide vari-

How to cite this paper: Aquilina, N. and Blundell, R. (2016) Biochemical and Physiological Effect of Silver Bioaccumulation. *Open Journal of Pathology*, **5**, 57-71. http://dx.doi.org/10.4236/ojpathology.2016.61008

ety of ways [2]. The metal is used in the production of cutlery, household utensils, jewellery and other decorative artefacts. Since the 20th century, silver and its compounds have also been crucial in the photographic and electronic industries [3]. This factor has led to changes in the levels of environmental silver because industrial waste contains increasingly high amounts of silver residue. With an increased level of silver in the environment, members of the animal and plant kingdoms have experienced a greater incidence of contact with contaminated food and water sources [4]. This has led to increased potential for bioaccumulation of silver in plants, animals as well as in humans. Apart from the increased presence of silver in our natural environment, another relatively new source of silver bioaccumulation in humans has been found to be silver nanoparticles used in medicine [5].

Naturally, this precipitates a number of physiological and biochemical effects which quite often result in adverse effects and pathologies [6]. The aim of this essay is to present the recent developments in the relationship between silver bioaccumulation and the physiology and biochemistry of living organisms.

2. Bioaccumulation through Food Chains

In order to affect human biochemistry and physiology, silver must fist find its way the body. This is possible because of transfer along food chains which leads to bioaccumulation.

2.1. Bioaccumulation—A Definition

Bioaccumulation is a process by which organisms absorb toxic chemicals from their environment or diet. The rate of absorption of the toxic substances surpasses the rate of elimination of the chemicals. This causes a concentration of the concerned chemical to remain in the organism, eventually leading to gradual accumulation [6]. Since the chemicals taking part in bioaccumulation are often toxic, the increase in an organism's concentration of the substance can easily lead to an increased risk of poisoning. This poisoning exerts its action by changing and affecting the normal physiology and biochemistry of the organisms involved. Therefore, bioaccumulation has effects both on a molecular and on a large-scale level.

The process of bioaccumulation not only causes a high degree of toxicity in the organisms which directly ingest or absorb the chemical substance. Every organism in the environment forms part of food chains and food webs. Through these biological interactions, concentrations of the toxic substances are transferred to different organisms, such that organisms which are not directly exposed to the chemical are also prone to bioaccumulation [7]. However, when higher organisms prey on affected organisms, the toxic chemicals tend to accumulate to a much greater extent in tissues. This increase in substance concentration is known as biomagnification [8]. The term biomagnification is reserved for terrestrial organisms since there is not enough evidence to support its importance in aquatic and marine organisms.

2.2. Silver in the Natural and Artificial Environment

Metallic silver is amongst the commonest metals used in everyday life. It may originate from natural sources or artificial sources.

In the context of the artificial environment, silver is quite often used in the photography and jewellery industries. Silver is used as a catalyst for a number of chemical reactions in industry [9]. This includes the conversion of methanol to formaldehyde and the conversion of ethene to oxirane. Oxirane is used principally in the textile industry. Industrial plants have been found to be the main contributors to artificial sources of silver in the environment. It is also known that industry makes use of compounds of silver as well, such as silver nitrate (V) and halide salts of silver in photography [10]. Other important sources of silver in everyday life include commonly used food colourings, various food preservatives [11] as well as dental tooth fillings [12].

An artificial source of silver which is constantly evolving and being innovated upon is nanotechnology. This involves the use of silver nanoparticles (AgNPs). It has been shown that these nanoparticles have vast antiviral and antimicrobial effects when applied to medicinal use [13]. This biocide action of AgNPs occurs because the nanoparticles release ionic silver into the bacterial or virally-infected cells once taken up by the same cells [14]. The silver ions then exert a range of toxic biochemical effects inside the cell, as will be discussed in the following chapters. However, it has also been shown that the use of these AgNPs brings about a wide plethora of toxic events not only in the pathogenic cells, but also in human body tissues. This is due to the fact that the transport of AgNPs to their target sites of action is difficult to regulate and specifically be pin-pointed [15].

Silver has been used as a treatment for a collection of psychiatric disorders, including epilepsy and addiction. The metal and its salts have also been used to treat infections such as gastroenteritis and gonorrhoea [16]. Silver nitrate (V) is an agent which is commonly used in the treatment of burn patients [17]. Therefore, humans working in the medical field and patients experience a high degree of contact with silver. This creates a window of opportunity for bioaccumulation to occur. The metal has also been historically applied to use in natural remedies believed to cure herpes infections, malignant tumours and acquired immune deficiency syndrome (AIDS) [18]. This has been found to be another source of silver predisposing people to silver bioaccumulation.

In nature, silver is found as ores and deposits in mines. The metal ores have been shown to dissolve in trickling water and wash downstream, thus spilling into the open environment [19]. Dissolution of the ores releases the silver as free silver ions (Ag^{+}). These free silver ions have been found to be highly toxic. However, it has also been documented that the water molecule itself forms complexes with the free silver ions, thus reducing their effective toxic properties [20]. This contrasts with the case of artificial silver sources because silver compounds used in industry, such as silver nitrate (V) and silver chloride, have been found to exert a greater extent of toxicity to organisms than the free silver ions in water [21]. Aside from exposure to the metal, another factor which has been found to contribute to silver bioaccumulation is its slow rate of excretion. Studies have shown that compared to the rate of silver particle intake, the rate of silver particle elimination was quite low [6].

2.3. Bioaccumulation in Fungi and the Plant Kingdom

The very first members of any food chain, the producers, mainly belong to the plant kingdom. Producer organisms rely on soil as a medium for obtaining nutrients such as electrolytes and water. These are needed to carry out the process of photosynthesis. Plants have been shown to take up silver via their roots [22]. However, the same studies have also shown that silver tends to accumulate in the roots themselves, meaning that the metal does not traverse or localise in other regions of the plant [23]. Using crops as a reference, the concentration of silver present in the above-ground parts of the plants was found to be less than 1 mg/Kg while that beneath the ground (roots) was found to range from 2.0 to 33.8 mg/Kg [24].

Additionally, crops grown for agricultural purposes have been found to accumulate much higher concentrations of silver than other well-studied plants [24]. Members of the kingdom fungi have demonstrated an exceedingly high potential to accumulate silver. This was shown by studies in which fungi were grown on silver sludge [25]. Recent literature has revealed that the metal does not interfere with the growth process of plants. This is illustrated by experiments carried out on common agricultural crops [24]. Even though silver has been found to exert antimicrobial effects when present in manure and sludge, the same studies have shown that it does not interrupt the fertilising properties of these mixtures. However, it does tend to progressively accumulate in the crops and fungi, especially in the case of lettuce and mushrooms. This was shown by the increased weight of lettuce leaves in a variety of experiments [24]. In conclusion, members of the plant kingdom effectively accumulate silver, resulting in bioaccumulation in herbivores as well as organisms at higher stages in food chains.

2.4. Bioaccumulation in Aquatic Animals and Algae

Trace metals have always been a topic of interest when studying aquatic and marine ecosystems. Silver has been found to be the metal with the highest uptake constant in these ecosystems [26]. It has also been shown that this depends on a number of physical factors. For example, absorption has been shown to be greater in regions of low salinity and low temperature [27].

In the case of marine and aquatic ecosystems, plants do not usually form part of the producer stage in food chains. It is the algae who take up this role. Research has shown that algae have the ability to efficiently absorb dissolved metal ions into their system. It has also been confirmed that silver ions are not only readily absorbed by the organisms, but the absorption proceeds at a very rapid rate [28]. This naturally leads to bioaccumulation in algae. Experiments have also shown that the use of enzymes, lowering of cellular pH and physical disruption of the algal cells failed to extract and detach silver from the cells [28]. The reason behind this is the fact that the metal undergoes chemical remodelling inside the cells. Experiments have also revealed that dead algal cells retain the ability to absorb silver from the surrounding environment. The dead algal cells will eventually form sediment [29]. Sediment is a dietary source for numerous aquatic organisms.

It has been stated that the reason behind silver bioaccumulation in organisms higher up the aquatic food chain is most likely due to its absorption by filter feeders [30]. Silver and its compounds have been shown to deposit and bind to sediment with a rather high affinity [31]. Filter feeders are invertebrates which constantly ingest and digest sediment. Sediment has been found to be a permanent source of silver in the aquatic ecosystem [31]. This is because of the exoskeleton of various invertebrates which binds to silver and, as previously stated, algal cells. Sediment is an active contributor to bioaccumulation. Studies have shown that filter feeders and other aquatic organisms rapidly absorb silver via their intestinal system and their gills [32]. Mussels have been used as model aquatic organisms in bioaccumulation studies. It has been noted that these organisms absorb silver and accumulate it effectively [33]. This is, of course, of great importance since mussels are a dietary source of a multitude of organisms, including fish and humans.

Organisms which have also been found to effectively bioaccumulate silver are oysters, clams and shrimp, all of which form part of the typical human diet [34]. With regards to the potential for fish to accumulate silver, it has been shown that other trace elements such as zinc and copper effectively increase the amount of silver accumulated by fish [35]. It has also been shown that silver interferes with the bioaccumulation process of mercury by decreasing its accumulation. Another reason behind the tendency of fish to accumulate silver has been shown to be the ability of fish gills to readily take up silver [36]. However, further studies are yet to be carried out to confirm the true role of fish in silver bioaccumulation.

2.5. Bioaccumulation in Terrestrial Animals

Vertebrates and invertebrates have been found to play different roles in silver bioaccumulation [6]. The silver reaches these higher organisms by way of contaminated producers which bioaccumulate the metal or by preying on consumers which feed on the producers. Regardless of the wide variety of routes by which silver can come into contact and enter the biological systems of the organisms, terrestrial animals have been shown to have a low absorptive potential for silver. However, even though the amount of silver taken up by the animals is relatively low, the metal tends to deposit readily in tissues [37]. This prevents the metal from being eliminated, thus leading to bioaccumulation.

Experiments using earthworms have shown that when exposed to silver levels present in industrial sludge, the organisms lost their ability to reproduce and they effectively accumulated the metal [21]. Pinnipeds (seals) have been shown to actively accumulate silver in their body, especially inside their fur and liver. These organs are used by humans for food and clothing [38]. Terrestrial molluscs, such as edible snails, have also been found to accumulate considerable amounts of silver metal in their tissues [21]. Studies on rats have shown that silver is found stored in particular organs, namely the liver, kidney and skin [37]. Birds have been found to bioaccumulate silver at very high concentrations [39]. Harmless concentrations of silver have also been detected in cow milk, beef meat, pig meat and sheep meat [6]. However, even the higher concentrations in these foodstuffs have been determined to be harmless. This means that the typical human diet does not consist of silver-bioaccumulating organisms. Therefore, after reviewing considerable literature, it can be stated that the main window of opportunity for bioaccumulation to occur in humans is via the presence of affected aquatic animals in one's diet.

3. Reasons and Mechanisms behind Silver Toxicity

Silver bioaccumulation leads to dangerous concentrations of silver being stored in biological systems. However, the metal itself exerts different extents of toxic effects depending on the organism and its environment.

First of all, as stated in previous chapters, the harmful actions of silver are due to its ability to form monovalent free silver (I) ions, Ag^+ [6]. It is very easy for the metal to produce these cations. This is because the lone electron in the last orbital of the silver atom is atomically distant from the positive nucleus, so the electrostatic attraction of the nucleus is diminished [40]. Additionally, there is repulsion from the other electron-rich orbitals. Free ions are known to be highly reactive. They are able to form complexes with a wide range of anions and molecules. This is achieved by means of various chemical bonds. The free silver ions have been shown to be able to interact with any cellular compartment capable of undergoing chemical reactions. Living cells may be likened to pools of water in which chemical reactions constantly occur. Therefore, it is no surprise that the reactive silver ions have multiple levels at which toxicity may be brought about, most notably in the cell's metabolism, genetic architecture and supportive structure [41].

Water can form complexes with a wide variety of metallic elements. It has been shown that when water molecules form complexes with silver ions, the toxicity of the metal ions is greatly buffered [42]. Another ion which has been shown to reduce the poisonous effects of silver ions is the chloride anion [43]. This explains the reason behind the diminished toxic events observed in aquatic organisms inhabiting regions having high salinities. Some organisms, especially fish, have been found to be resistant to the effects of silver ions because of the involvement of other ions [35]. Silver is found at a lower level than the ions of sodium and calcium in the electrochemical series. Since silver and calcium ions are much more common than silver ions, they tend to displace the silver ions, rendering them inactive [40]. Studies have indicated that this is probably the reason behind the lack of silver toxicity in bioaccumulating organisms like bivalves [44]. However, this is not always the case. In some situations, namely in the case of terrestrial organisms, there are no such molecules present to protect animals and plants from silver ions. The free silver ions are able to participate in a number of reactions taking place in the organisms. The precise molecular mechanisms behind these actions of the silver ions will be described in the upcoming chapters.

4. Biochemical Effect of Silver Bioaccumulation

Silver is capable of undergoing reduction and oxidation reactions. It is known to play a role in the production of reactive oxygen species (ROS) in cells possessing mitochondria [45]. These ROS react and damage other cellular organelles and molecules such as DNA. This phenomenon is known as oxidative stress, and it has been shown to be one of the major mechanisms by which silver leads to toxic effects in the body.

When considering cellular genetics, experiments on various bacterial cells have shown that silver ions interact with DNA [41]. The DNA was found to condense and form granules when exposed to silver ions. These interactions made the DNA lose its ability to replicate and express genes, preventing cells from dividing and proliferating. Aside from direct damage to DNA, it is now known that silver ions have the potential to trigger the expression of a number of genes related to apoptosis [46]. Studies have revealed that this action is achieved via activation of genes which initiate the mitochondrial pathway of apoptosis. Silver causes a conformational change in the BAX gene (regulator of apoptosis) which causes it to migrate to mitochondria, thus commencing the process of apoptosis. There is also evidence that silver ions interact with caspases, leading to apoptosis [47].

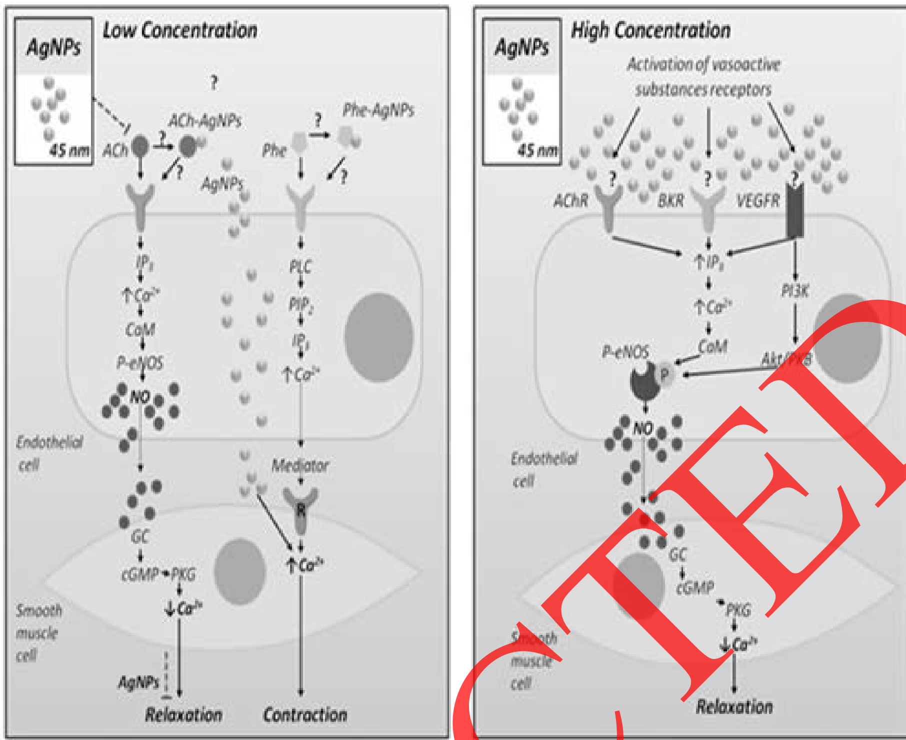
It has also been found that silver damages the mitochondrial complexes forming part of the electron transport chain in specific tissues, namely brain and skeletal muscle [48]. This affects the production of energy in the form of adenosine triphosphate (ATP) in the cells, thus leading to cellular death by necrosis. In the case of brain cells, the lack of ATP blocks the function of the energy-dependent ion channels on cell membranes. This has been confirmed to inhibit the generation of electrical signals in brain cells.

Research has shown that proteins interact with silver, leading to disruption of their normal organised structure [49]. The metal has been shown to do this by means of two main mechanisms. Silver ions readily form complexes with hydrogen ions found at the carboxyl end (C-terminal) of the proteins (COOH giving COO^- and H^+). This complexion of hydrogen ions has been shown to bring about conformational changes in the protein. Aside from this disturbance in protein structure, silver has also been demonstrated to bind to the thiol functional groups of cysteine and methionine amino acid residues along polypeptide chains. Therefore, normal protein structure is further disturbed.

Another biochemical effect of silver which has been recently discovered is its activation of muscarinic receptors [50]. These receptors bind the neurotransmitter acetylcholine (ACh) in order to initiate signal transduction in the cell. In an experiment on rat tracheal smooth muscle, the results show that the binding of silver to the muscarinic receptors leads to high levels of nitric oxide (NO) production in the airway smooth muscle cells [50]. It is known that NO production in the normal physiological context is ACh-dependent. The study has shown that when silver binds to the receptor, NO production is ACh-independent. The signal transduction initiated by silver binding has also been demonstrated to induce the expression of an inducible isoform of the enzyme nitric oxide synthase (iNOS). Additionally, the same study has revealed that signal transduction relies on the activation of the enzyme phospholipase C (PLC). This is all shown in **Figure 1** and **Figure 2**.

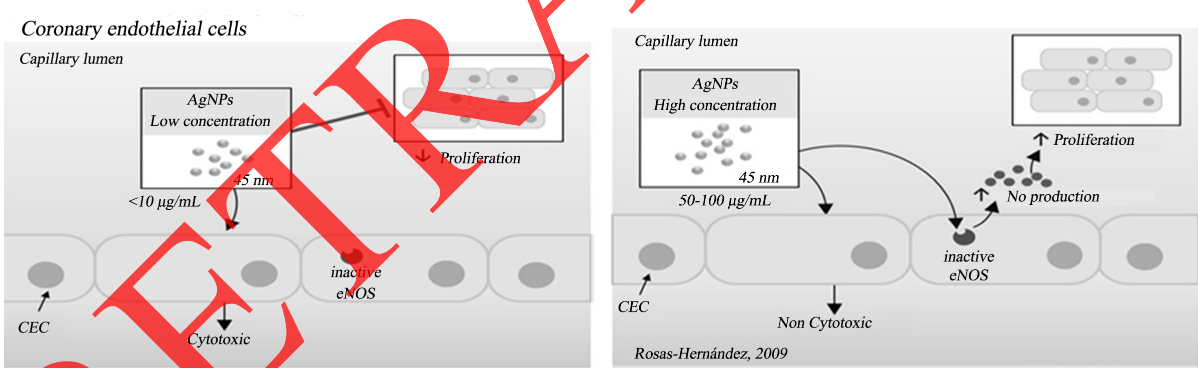
By means of this mechanism, silver exerts a negative effect on cellular proliferation. In the same experiment, it was found that silver-induced production of NO causes the excess NO to bind to extracellular signal-related kinases (ERKs). This nitration was specifically found to take place at the thiol residues of cysteine and methionine [51]. Nitration of these proteins was shown to lead to NO-induced inhibition of cellular division with apoptosis (programmed cell death) being triggered.

Silver also plays a role in the vascular endothelial growth factor (VEGF) transduction pathway [15]. VEGF normally gives rise to the synthesis of new blood vessels (angiogenesis). Silver also gives rise to such an effect.



(a) (b)

Figure 1. Interaction between AgNPs and Muscarinic Receptors. Low concentrations are shown to cause muscle contraction while high concentrations are seen to bring about muscle relaxation.



(a) (b)

Figure 2. Diagrams showing the action of different concentrations of silver on coronary endothelial cells. (a) Low concentrations inactivate iNOS and thus prevent NO-dependent proliferation; (b) Higher concentrations activate eNOS and induce NO-associated proliferation of the cells.

This has been shown to occur since silver increases the level of phosphorylation of ERK proteins [52]. These then stimulate endothelial nitric oxide synthase (eNOS) to produce NO. This NO produces vasoactive effects, including cellular proliferation. **Figure 3** illustrates the interaction between the VEGF pathway and silver nanoparticles.

5. Physiological Effect of Silver Bioaccumulation

The previously discussed biochemical effects of silver bioaccumulation manifest as physiological effects. Studies have shown that silver is rapidly transported throughout the circulatory system to be deposited in a spectrum

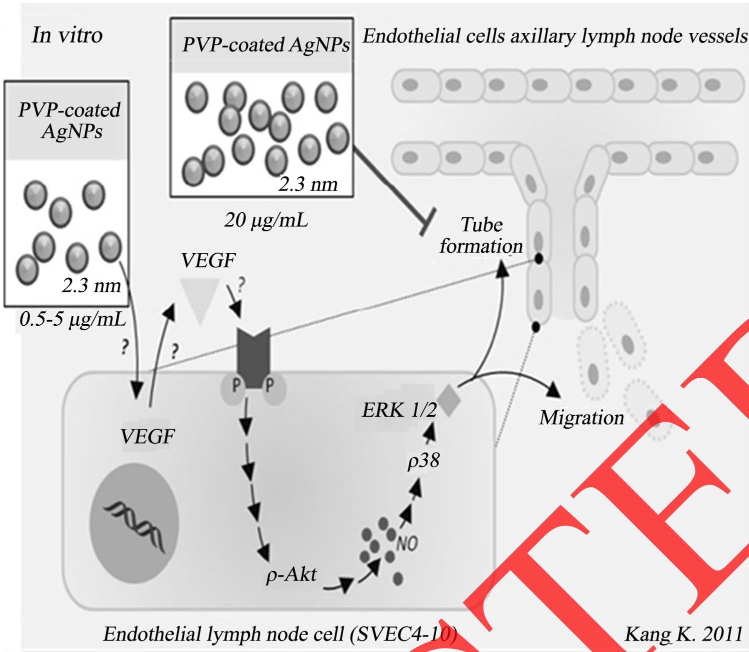


Figure 3. Diagram showing the mechanism behind the activation and inhibition of angiogenesis brought about by different concentrations of AgNPs. Low concentrations promote angiogenesis while high concentrations oppose it.

of body tissues [53] [54]. In the circulation itself, studies have shown that silver leads to vasodilation of coronary vessels as a result of NO production [15]. The effect depends on concentration, and it was found that low concentrations of silver trigger vasoconstriction while high concentrations trigger vasodilation. This is shown in **Figure 4** and **Figure 5**.

Silver has been shown to induce cellular adaptations in the cardiac myocytes of the left ventricle in rats, resulting in left ventricular hypertrophy [55]. This enlarged heart phenomenon can also be seen in studies carried out on turkeys [56] [57]. Aside from hypertrophic effects, the turkeys and rats being examined in the research study were also found to have an increased number and volume of red blood cells (haematocrit) and increased haemoglobin concentrations. Slight changes in the elastin network of the walls of the aorta were also found.

Research has shown that silver ions emerging from silver nanoparticle bioaccumulation induce destruction of red blood cells [58]. Red cell lysis gives rise to a state of anaemia. They have also been found to disturb the function of plasma carrier proteins such as albumin [59]. The ions trigger the release of alpha granules from platelets [60]. These contain clotting factors and proteins, meaning that silver leads to blood coagulation. However, silver has been found to promote inflammatory processes by increasing leukocyte adhesion and inducing their proliferation [61]. This is one of the reasons why it acts as an adjuvant in vaccines. This is all illustrated in **Figure 6**.

It has been shown that silver forms deposits in the basement membranes of renal glomeruli [53] [54]. The same research has shown that the metal does this with a very high affinity. The reason behind this high affinity for deposition in glomeruli is yet to be discovered. The renal system is of crucial importance in the regulation of blood pressure. Therefore, if the normal physiology of the kidney is impaired, the body's blood pressure will be considerably raised, a factor known as hypertension. The filtration of blood plasma is considerably impaired [62]. The progressive drop in glomerular filtration rate (GFR) will eventually lead to an increase in blood plasma volume, giving rise to hypertension. Hypertension itself is known to have harmful effects on vessel walls. It is one of the main causative agents of cerebrovascular stroke and heart failure [63].

Not all physiological effects of silver bioaccumulation are negative, however. Administration of silver nanoparticles has been shown to increase the blood flow in blood vessels, especially those which were newly formed by means of silver-induced angiogenesis [15]. Therefore, silver (especially when present at high concentrations)

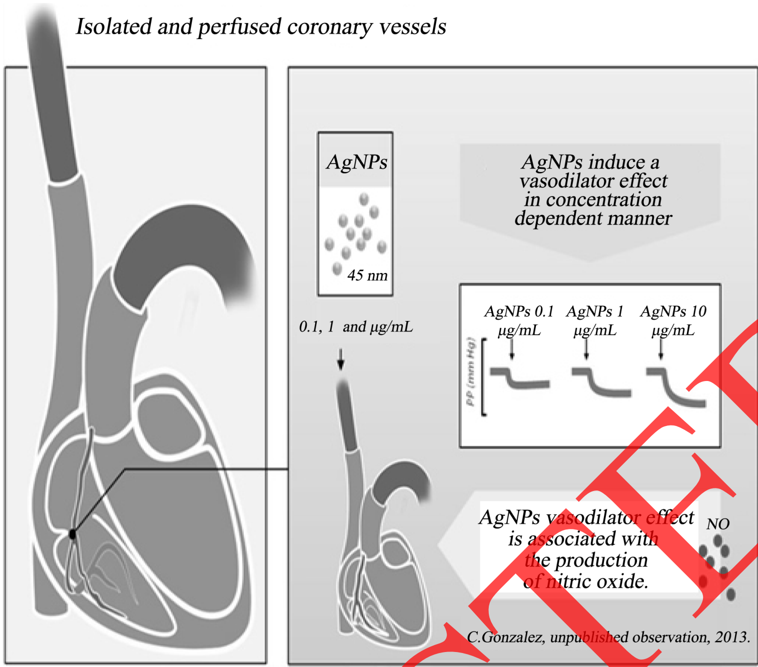


Figure 4. Physiological result of silver interaction with coronary vessels. High concentrations of the metal induces NO formation and vasodilation of the vessels.

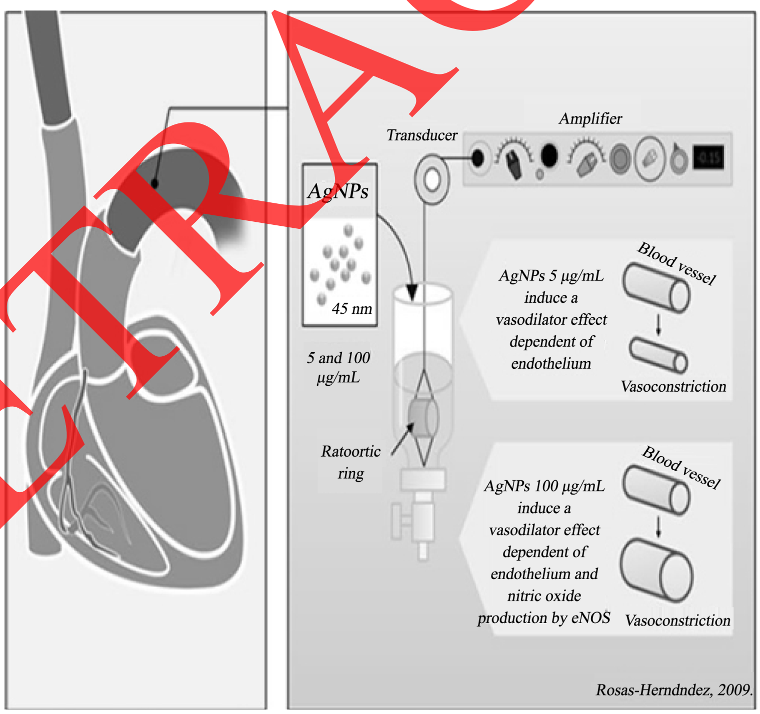


Figure 5. Diagram showing the contrasting effects of silver on the aorta. Low concentrations cause Vasoconstrictions while higher ones lead to vasodilation of the arteries.

increases the vascularisation and blood flow of tissues.

It has been confirmed that silver and its compounds also affect the normal physiology of the respiratory system

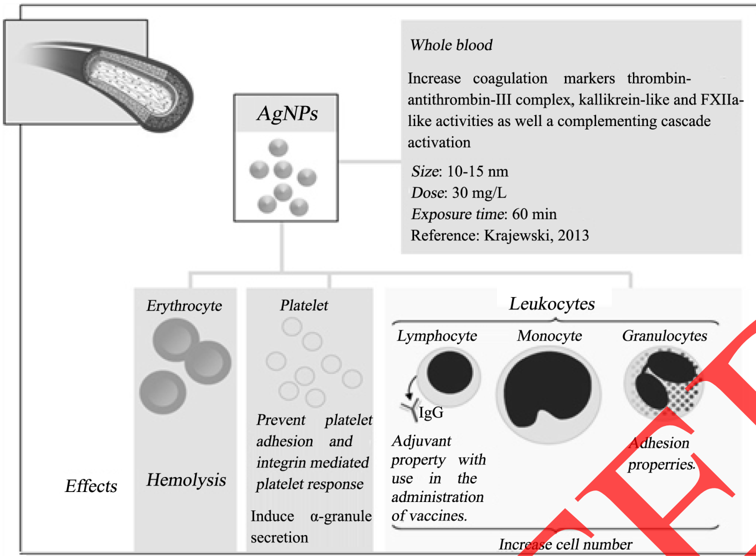


Figure 6. Figure showing the effects of silver on the cellular fraction of blood. The metal causes red cell lysis and white cell proliferation. It is also associated with thrombus formation due to its action on platelets.

[64]. Studies have shown that once silver particles are inhaled from the surrounding environment, macrophages found in lung alveoli use phagocytosis to keep the alveoli clear of the debris, thus preserving efficient gaseous exchange [65]. However, research has revealed that silver is highly cytotoxic to macrophages, smooth muscle cells and epithelial cells lining the respiratory tract [66]. It has been shown that when the macrophages are damaged, pro-inflammatory cytokines (PICs) are released into their surrounding environment. These cause the airway smooth muscle to contract, thus bringing about a state of asthma. This may lead to suffocation. Furthermore, silver has been found to possess the ability to cross the blood-gas barrier of the alveoli [66]. This makes the airways another route for silver distribution throughout the body.

In the case of the nervous system, literature has shown that silver forms vacuoles in the tight junctions (TJs) of endothelial cells forming the blood-brain barrier (BBB) [67]. The role of the BBB is to prevent harmful chemicals from reaching the central nervous system. If the BBB is disrupted, toxic substances can reach the brain and harm the central neurons. Evidence suggests that the disruption of TJs by silver causes the release of PICs, indicating cell death and increased BBB permeability. However, silver nanoparticles coated with citrate ions do not produce such an adverse effect [68]. This indicates that once again, the toxic potential of silver lies in its free ions. Additionally, brain tissue has been revealed to retain silver for very long periods of time [69]. Even though this physiological effect shows that silver bioaccumulation is most probably involved in a number of neurological disorders, further research is yet to be carried out.

Rather recent research has shown that silver nanoparticles induce apoptosis in male Sertoli and Leydig cells [59]. Both cell types are involved in the process of spermatogenesis. Therefore, if these cells fail to carry out their function, the bioaccumulating male is subjected to infertility.

6. Medical and Clinical Aspect of Silver Bioaccumulation

If chronically exposed to silver and its compounds, one tends to develop argyria; a bluish-grey colouration of the skin [39]. The condition arises because of silver being deposited in mucous membranes [70]. This is seen by the micrographs in **Figure 7**. However, evidence suggests that the recolouration of the skin is most likely due to the interaction between silver and melanocytes (the pigment-producing cells of our skin) [71]. Some areas tend to be darker in colour. Research suggests that when exposed to light, silver is chemically reduced to give this darker blue shade. The same study has shown that even if exposure to silver is stopped, the patient's argyria still persists. Patients are however warned to use appropriate protection and avoid long periods in the sun. The following signs and symptoms are characteristic of argyria and are thus used for its diagnosis [72]. Some symptoms are also illustrated in **Figure 8** and **Figure 9**.

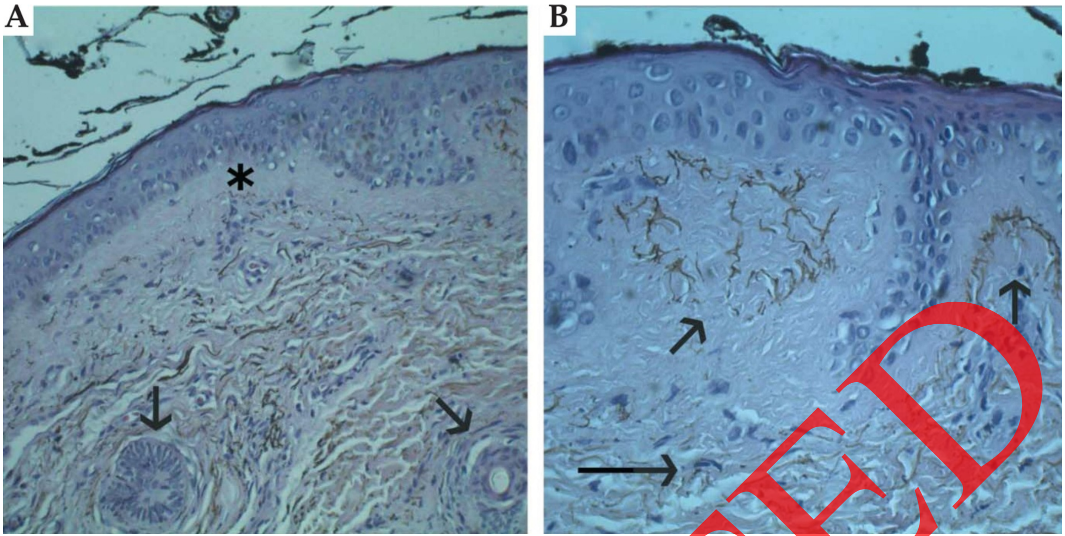


Figure 7. Micrographs depicting silver deposition in mucous membranes © Enei *et al*. 2013. The * in (A) shows a normal membrane while the arrows point towards pigment cells. In (B), the arrows show that silver (brown lines) has been deposited in the tissue and pigment cells have taken the metal up.

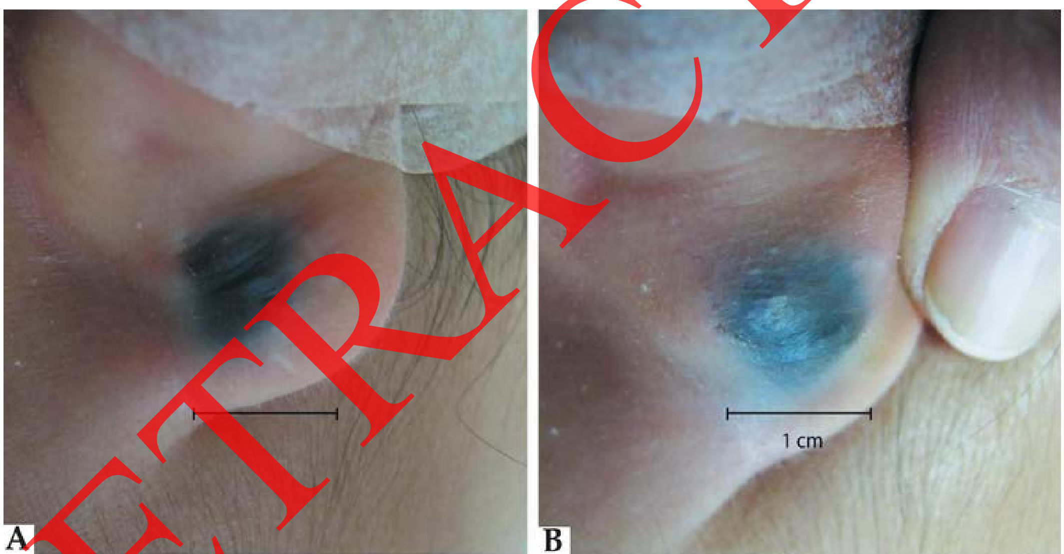


Figure 8. Pictures showing typical argyria of the ear lobule after contact with a silver earring ©Enei*et al*. 2013. Note the bluish-black tinge of the skin.

- Fingernails change their colour to blue.
- Elevated serum silver levels (greater than 5.0 mcg/L).
- Loss of sight due to the lens being affected.
- Normal-coloured sclera and conjunctiva.

As mentioned in previous chapters, silver bioaccumulation is known to give rise to hypertension. Hypertension has pathological effects on both cardiovascular and renal systems. In the renal system, hypertension destroys renal glomeruli [53] [54]. This leads to renal failure. In the cardiovascular system, hypertension is known to cause the formation of atherosclerotic plaque in vessel walls [62]. This is furthered by thrombus formation and embolus release. The embolus may dislodge in the pulmonary circulation or cerebral circulation, leading to sudden death. Hypertension is also a major cause of heart failure in the western world [73].

Silver bioaccumulation is known to cause anaemia [58]. This condition is the result of a decreased red blood cell count and therefore a decreased oxygen load being delivered to metabolising cells. Patients with anaemia

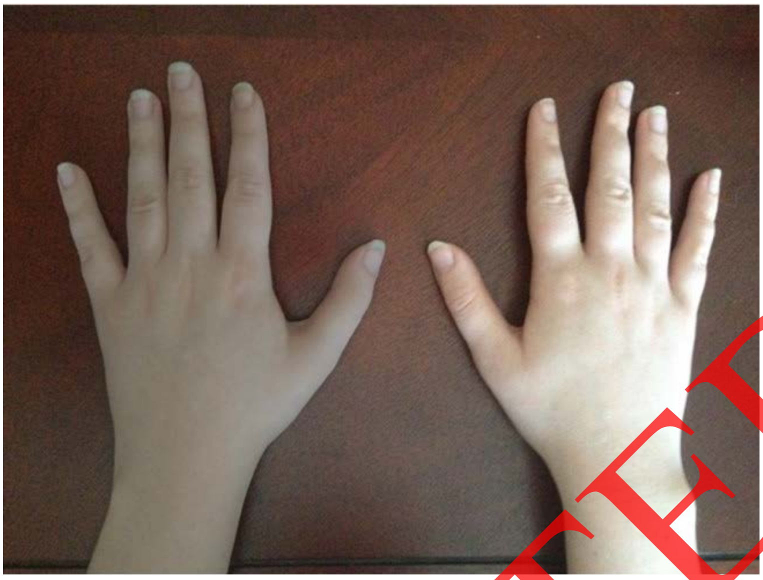


Figure 9. Contrasting a normal skin colouration (right hand) with that of an argyria patient (left hand) ©Hayward 2014. Note the grey fingernails and darker skin tone of the left hand.

present with lethargy and weakness, and if this condition persists, body tissues undergo necrosis and death due to the lack of oxidative ATP production. Bioaccumulation of the metal has been implied to precipitate neurological diseases. Silver has also been shown to give rise to infertility [59]. This is due to its ability to deposit in testis with a high affinity. Inhaled silver particles have been shown to cause obstructive pulmonary disease and asthma by their action on airway smooth muscle [50], but further investigations are yet to be carried out. Future studies will also focus on the use of silver nanoparticles as an anti-cancer agent due to the metal's apoptotic capabilities.

Current research points towards the use of the algal special *C. marina* for treatment of silver bioaccumulation [74]. The basis of the treatment is the fact that algal cells are able to readily take up the metal from their surrounding environment [28]. The human body cannot bioaccumulate the metal in this way because, as explained previously, it has been found that silver cannot be detached from algal cell walls and membranes [28]. Additionally, the algal cells themselves cannot cause harm to the human body because they are rendered inactive once taking up metallic silver. The algal cells will then be excreted by the human body [75].

7. Conclusion

It is well documented that the environmental levels of silver are on the increase. It is also evident that humans not only come into contact with the metal via bioaccumulation from food chains, but one also encounters the metal in medication and tools used in everyday life. Man is most likely to bioaccumulate silver from diets consisting of affected fish or from the constant dosage of medication containing the metal. Studies have shown that silver does induce cellular apoptosis. Silver is also known to have harmful effects on the cell's genetic material. It also interacts with cell receptors, thus interfering with cell signalling. The metal's toxicity leads to problems in the cardiovascular, renal and respiratory systems as well as the nervous system and reproductive system. Treatment for bioaccumulation of silver is still not readily available. However, recent studies have shown that the alga *C. marina* can be used to effectively eliminate the metal and its ionic forms from the human body.

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