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Review

Silver nanoparticle fate in mammals: Bridging *in vitro* and *in vivo* studies

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ABSTRACT

Silver nanoparticles (AgNPs) are exponentially used in various consumer products including medical devices. This production leads to an increasing human exposure to silver in different forms. Indeed, AgNPs are subject to various transformations in aqueous aerobic conditions that trigger the production of Ag(I) species. The main environmental transformation produces the non-toxic species silver sulfide. Transformations occurring in mammals are more diverse and mainly depend on the interaction of AgNPs with thiol, chloride and proteins. Any of these species have a different impact on AgNPs and induces AgNP dissolution into Ag(I) species, aggregation and/or stabilization. The transformations occurring also depend on the exposure route. The main one is dietary but medical exposure is also growing with the massive use of nanosilver as biocide in medical devices. For the former, AgNP modifications and Ag distribution has been extensively studied using *in vitro* and *in vivo* models, while data related to medical use of nanosilver are scarce. However, most of the *in vitro* and *in vivo* data often remain inconsistent. In this review, we describe both *in vitro*, *in cellulo* and *in vivo* data about AgNP transformations, silver speciation and biodistribution. We try to reconcile all these data and describe the latest methods for the future studies of AgNP fate in mammals.

Contents

Abbreviations: 3MPS, 3-mercapto-1-propanesulfonate; AF_4, asymmetrical flow field-flow fractionation; AgNM, silver nanomaterial; AgNP, silver nanoparticle; Ag_2S, silver sulfide; BSA, bovine serum albumin; CRM, confocal reflectance microscopy; CSE, cystathionine γ-lyase; Ctr1, copper uptake protein 1 ; Cys, cysteine; EDX, energy dispersive X-ray spectroscopy; EFSA, European Food Safety Authority; EMSD, elemental mass size distribution; FIB-SEM, focused ion beam – scanning electron microscope; GCLM, glutamate cysteine ligase modifier; GIT, gastro-intestinal tract; GSH, glutathione; IgG, immunoglobulin G; JRC, joint research centre; K_{sp}, solubility-product constants; MT, metallothionein; MTF1, metal regulatory transcription factor 1; NLS, nuclear localization signal; PCR, polymerase chain reaction; PDI, polydispersity index; Pen, Penicillamine; PVP, polyvinylpyrolidone; ROS, reactive oxygen species; SERS, surface-enhanced Raman spectroscopy; SIM, structured illumination microscopy; SOD1, superoxide dismutase 1; SP-ICP-MS, single particle inductively coupled plasma mass spectrometry; SPR, surface plasmon resonance; STEM, scanning transmission electron microscopy; TEM, transmission electron microscopy; XANES, X-ray absorption near edge structure; XAS, X-ray absorption spectroscopy; XRF, X-ray fluorescence.

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1. Introduction and background

1.1. Silver nanomaterial generalities

Silver is used as biocide since antiquity, and its "nano" form has been developed and increasingly used since the nineties [1]. Silver nanomaterials (AgNMs) are widely used to preserve consumer and medical products thanks to their prolonged release of Ag(I) species, *e.g.* in clothing [2], home appliances [1], food industry [3] as well as in medical fields [4] (for review see [5]). Moreover, the physical properties of AgNMs, photophysical in particular, also lead to their increased use for various applications: sensors [6–9], electronic devices [10], etc. Various Ag shapes can be produced, rods, stars, wires [11], plates, but the most common is probably the sphere, named Ag nanoparticle (AgNP).

Whatever the shape, AgNMs are constituted of an Ag(0) core synthesized by the reduction of Ag(I) ions using chemical or physico-chemical processes [12,13]. The former process uses reductants such as citrate, alone or in the presence of additives that help to control AgNM size and shape [14,15]. The latter can be done by photophysical reduction for instance [16]. Alternative solutions, considered as greener processes, have massively developed in the last years (for review see [17,18]). They use cellular extracts from different organisms, such as plants or bacteria, to perform Ag(I) reduction in order to produce AgNMs. An organic coating, weakly bound to the surface, is generally added to stabilize these AgNMs. The most common coatings for conventional AgNPs are polyvinylpyrolidone (PVP) and citrate. The former is a polymer highly stabilizing the NPs by steric hindrance, while the latter is a small organic molecule in dynamic equilibrium with citrate in solution and therefore easily exchangeable.

A recent review highlights the complexity of metal speciation studies in biological fluids in cases of well-known metals, such as Cu and Pt [19]. AgNMs are also highly sensitive to the surrounding environment, and particularly to the redox potential of the media since oxidative conditions easily trigger the oxidation of Ag(0) at the surface of the material into Ag(I). On the contrary, Ag(I) can be reduced to Ag(0) under light illumination. Therefore, the high reactivity of Ag makes these AgNMs subject to a wide variety of transformations, especially under aerobic situation in aqueous media, typical of environmental and biological conditions [5,20]. The diversity of Ag species produced in these conditions makes difficult to perform relevant studies of AgNM toxicity. AgNPs are indeed subject to various transformations in the environment before organism absorption and the life-cycle of the nanomaterial has to be taken into account in toxicological studies. It has been described that sulfidation of AgNPs is the major process occurring environmentally [21,22] (for review see [23]). Several studies have quantified the release of AgNPs and Ag(I) ions from functionalized materials and consumer products such as textiles, food packaging or medical devices but they provide a very wide range of values from 10 μg up to 2 mg of released Ag per gram of product (for review see [5]). It is therefore difficult to use these information to direct study of their impact on Human and the environment. It also explains why the study of AgNM fate in environmental and biological media is still an intense field of research.

1.2. AgNP behavior in biological media and species-related toxicity

Nanotoxicology studies are also plethora [24–29] but the conditions used are rarely relevant to real exposure levels, as well as to the type of species organisms are exposed to (for review see