Environmental Toxicology and Pharmacology 40 (2015) 729–732

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

Mini-review

Toxicological effects of silver nanoparticles

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ARTICLE INFO

Article history:
Received 31 July 2015
Received in revised form 4 September 2015
Accepted 5 September 2015
Available online 11 September 2015

Keywords:
AgNPs
Biomedical
Healthcare
Toxic
In vitro
In vivo

ABSTRACT

Nanotechnology offers numerous biomedical applications and in so doing, exerts toxic effects. AgNPs, one of the metallic nanoparticles is known for its antibacterial applications and hence exposed to human through various healthcare products. Analysis of its toxic effects is necessary before its appliance into the biomedical field. Hence, this mini-review focuses on toxic effects of AgNPs related to human and his environment *in vitro* and *in vivo*.

Contents

1. Preface to AgNPs

Nanotechnology is a rapidly emerging field, with a funding across the globe in 2010 amassed at 17.8 billion dollars

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http://dx.doi.org/10.1016/j.etap.2015.09.003
1382-6689/

(Sargent, 2012). Industrial and household applications have led to the increased exposure of engineered nanoparticles to humans (Nowack and Bucheli, 2007). Among the engineered nanoparticles, silver exposure is the hit of highest point as it is used in medical implants (DeVasConCellos et al., 2012). Metallic nanoparticles are synthesized with the goal of drug delivery, treatment, diagnosis, monitoring, and control of diseases (Boldyreva, 2014). For these applications, approximately 55 tons of AgNPs are produced annually. By March 2011, the total number of nanoformulated consumer products was 1300, among which 313 were of silver. A sum of 7499 articles (59%) was published on applications of AgNPs (Bondarenko et al., 2013). Estimates indicate that 14% of total AgNPs used in consumer products are released into the air while they are utilized. They deposit in different regions of the respiratory tract and get displaced to different organs of the human body (Gonzalez et al., 2014).

2. Optimistic face of AgNPs

AgNPs are a multitude better in cytotoxic effects on cancer cell line evaluated against normal liver cell line (Faedmaleki et al., 2014). The liver is most probably the primary site for accumulation of AgNPs (Arora et al., 2009; Takenaka et al., 2001). It is capable of excreting the AgNPs, through bile, absorbed from GI tract. Since the liver cells showed relatively less effects as indicated by Faedmaleki et al. (2014), AgNPs could be a potential candidate for *in vivo* studies. Therefore, the biomedical applications of AgNPs vary from antibacterial, antiviral, antitumor applications to being applied as biosensors and biological labels (Huang et al., 2011). One such application is as an anticancer agent, in which the AgNPs induce cell death in human colon cancer cell lines by induction of apoptosis through the participation of p53 (Satapathy et al., 2013).

3. Toxicity of AgNPs *in vivo* in animal models

Though the AgNPs have potential biomedical applications, emphasis on nanotoxicology has made it an important field of research due to the impact it poses on the human environment (Mahmoudi et al., 2012). Biosynthesized AgNPs are less toxic compared to chemically synthesized AgNPs (de Lima et al., 2012).

AgNPs showed L(E)C50 values below 10 mg/L approximately to organisms such as crustaceans, fish and protozoa (Bondarenko et al., 2013). They were cytotoxic to rainbow trout cell lines and its hepatocytes (Connolly et al., 2015). Researchers also suggest that the release of AgNPs into the environment should be carefully monitored, based on the studies made on *Daphnia magna* (Asghari et al., 2012). *Eisenia fetida* was found to be affected by the toxic nature of AgNPs, which was size-dependent (Li et al., 2014). Zebrafish showed behavioral changes after exposure to AgNPs (Powers et al., 2011). Smaller sized nanoparticles were more toxic compared to their large sized counterparts (Liu et al., 2010). Toxicity studies on the embryo of zebrafish elucidated that the smaller sized nanoparticles (20 nm) were comparatively toxic to 100 nm AgNPs (Kim and Tanguay, 2014).

The toxicity created by AgNPs can be classified into three possible hypotheses. The first hypothesis suggests that in aqueous environments, the Ag ions released results in toxicity. Secondly, they may cause toxicity through metal ion independent mechanism. Thirdly, they remain as nanoparticles outside cells and release Ag ions as they dissolve inside cells (Poynton et al., 2012).

4. Toxicity of AgNPs against immune cells

AgNPs have no significant biological function in humans and therefore reach and cause damage to liver when exposed intravenously (Sandstead, 1995; Li et al., 2014a). They have been known to interact with human primary PBMC and increase oxidative stress in human neutrophils (Paino and Zucolotto, 2015). AgNPs of small size (10 nm) were found to be toxic to human blood mononuclear cells and the toxicity was both time- and dose-dependent (Barkhordari et al., 2014). Though the AgNPs were not clearly studied as an immunogen, they were able to produce an inflammasome when exposed to the human monocytes (Simard et al., 2015). On the positive side, they can modulate cytokines involved in wound healing (Tian et al., 2007).

5. Toxicity of AgNPs against normal human cell lines

5.1. Digestive system

AgNPs were shown to penetrate cell membrane and enter mitochondria leading to oxidative stress, inflammation and thereby leading to apoptosis when incubated with human gingival fibroblast cells (Inkielewicz-Stepniak et al., 2014). Treatment of AgNPs through oral route to mice resulted in impediment of function of small intestine mucosa due to destruction of microvilli. It was hypothesized that reduction in absorption by intestinal epithelium led to weight loss in mice (Shahare et al., 2013). Absorption through GI tract is the route through which nanoparticles achieve the entry to blood and in that way to the organs, when exposed orally (Bergin and Witzmann, 2013). The smaller sized AgNPs were accumulated more in organs such as brain, lung, liver, kidney, and testis compared to the larger sized AgNPs. Constant oral administration may lead to toxicity in the organs and inflammatory responses (Park et al., 2010). Similarly, another study states that AgNPs are toxic to mice *in vivo* as there were changes in histological sections of liver and apoptosis was induced (Al Gurabi et al., 2015).

5.2. Sensory organs

Toxicity study in rat ear model showed that the AgNPs exposure resulted in mitochondrial dysfunction leading to hearing loss, either permanent or temporary based on the dose (Zou et al., 2014). Even low concentrations of AgNPs have been absorbed by retinal cells and the structure was disrupted with increased number of cells under oxidative stress (Söderstjerna et al., 2014).

5.3. Respiratory system

Lung cell line treated with AgNPs resulted in size dependent toxicity, with 10 nm sized AgNPs being more toxic compared to larger sized particles (Gliga et al., 2014). ROS induction led to DNA damage and chromosomal aberrations in normal human lung fibroblast cells as studied by Asharani et al. (2009).

5.4. Urinary system

Kidney cell lines treated with AgNPs showed that cytotoxic effects were observed only in higher doses which show that accumulation inside the organ at higher doses might be the reason for toxicity *in vivo*. At limited dose, they are not cytotoxic to kidney cell lines *in vitro* (Milić et al., 2015).

5.5. Reproductive system

Spermatogonial stem cells were resistant to AgNPs of larger size comparatively to smaller AgNPs. This shows that size-dependence is a major criterion for toxicity of AgNPs on germ cell lines (Zhang et al., 2015). AgNPs compromised the embryo development as a