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The possible mechanism of silver nanoparticle impact on hippocampal synaptic plasticity and spatial cognition in rats

Ye Liu[a], Wei Guan[a], Guogang Ren[b], Zhuo Yang[a,*]

[a] School of Medicine, Nankai University, Tianjin 300071, PR China
[b] Science and Technology Research Institute, University of Hertfordshire, Hatfield, Herts AL10 9AB, UK

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ABSTRACT

Silver nanoparticles (Ag-np) are very promising engineered nanomaterials which play an important role in the world biomedical, healthcare and in general nanotechnology applications. With the most impressive effect in antibacterial and many other broad-spectrum biotechnological advantages, Ag-np in real applications is still a controversial issue. This study investigated effects of the Ag-np on hippocampal synaptic plasticity and spatial cognition in rats and followed with the research on their possible mechanism. In this study, twenty-four adult male Wister rats were randomly divided into 3 groups: control group, low-dose group (Ag-np, 3 mg/kg) and high-dose group (Ag-np, 30 mg/kg). After two-week exposure to Ag-np through the nasal administration, Morris water maze (MWM) test was performed for the spatial cognition, followed by the long-term potentiation (LTP) recording and reactive oxygen species (ROS) detection in hippocampal homogenate. Results showed that compared with the control group, both LTP and MWM were abnormal in low-dose group and high-dose group. The quantity of ROS in hippocampal homogenate was increased significantly in low-dose group and high-dose group, which may be the reason of the neural damage caused by Ag-np.

1. Introduction

The nanomaterial processing, characterization and application are one of the most prevalent technological developments in the last century. Today, nanometer materials have a wide range of applications in biological, medical and biochemical engineering fields. Generally speaking, nanoparticles have a diameter between 1 and 100 nm, so it is also called ultrafine particles. Because of their unique structures, nanoparticles have novel physical and chemical characteristics, and they show different properties from the conventional materials in many aspects. The silver nanoparticle has a broad-spectrum antimicrobial property, which encourages its use in biomedical applications, food production and a lot of consumer products. It is also used for the treatment of wounds and burns. Along with the rapid development of nanotechnology, the applications of nano-silver particles have been extended further and now silver is one of the most commonly used nanomaterials in many domains, such as some imaging and therapeutic purposes, medical implants, catheters and wound dressings (West and Halas, 2003; Chen and Schluesener, 2008). The more popular use of nano-silver products becomes, the more widespread exposure potential will be to human beings and environments.

Therefore, the toxicity of silver nanoparticles has been studied in different mammalian cell lines, including rat liver cells (Hussain et al., 2005), human keratinocytes and fibroblasts cultures (Burd et al., 2007), and human spermatogonial stem cells (Braydich-Stolle et al., 2005). To our knowledge, two studies have so far investigated in vivo about the toxicity of nanosized silver, one is performed by Sung et al. (2008), and the other is by Kim et al. (2008). The former study showed that lung function was reduced, and inflammatory lesions could be seen in lungs of rats during 90 days of inhalation exposure to silver nanoparticles, while the later one tested the oral toxicity of silver nanoparticles (60 nm) over a period of 28 days in Sprague-Dawley (SD) rats, and consequently the silver nanoparticles were found accumulated in the olfactory bulbs of SD rats and also accumulated in the brain. Hence, these results brought us much doubt on whether silver nanoparticles (Ag-np) can cause some neurotoxicity in human and animals. These suggest more studies are needed to determine the exact neural impact or risk on the levels of exposure to the Ag-np and the possible mechanism thereof. Previous studies showed that Ag-np in vitro induced liberation of reactive oxygen species (ROS), and the elevated mount of free radicals, which could lead to the oxidative stress, may be accounted for the cytotoxicity (Arora et al., 2008). The study has therefore been designed to focus on the neurotoxicity of the Ag-np and its possible mechanism in rats.

* Corresponding author at: School of Medicine, Nankai University, No. 94 Weijin Road, Tianjin 300071, PR China. Tel.: +86 22 23504364; fax: +86 22 23502554.
E-mail address: zhuoyang@nankai.edu.cn (Z. Yang).

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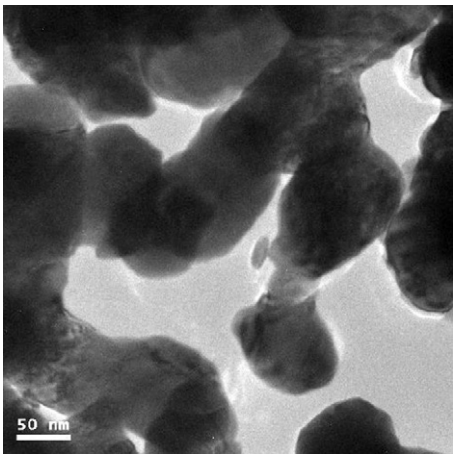

Fig. 1. TEM image of nano-scaled Ag in suspension.

2. Materials and methods

2.1. Silver nanoparticles

The nano Ag particles were produced in plasma process by QinetiQ Nanomaterials Ltd, UK. The plasma technology uses extremely high temperatures (over 10,000–100,000 °C) to vaporize microscaled particles in the up stream. And then in the down-stream the vaporized gas was cooling down by injecting the inactive gases to condense or to consolidate the gas vapour into nanoscaled metal or metal oxide nanoparticles. The process is managed in a way that nanoparticles will be formed in a designed way and controllable way. And plasma process does not need to use any additive solvent or solution; therefore it produces very pure or uncontaminated materials. Ag-np was provided by Research Institute of Science & Technology (RSTI), University of Hertfordshire, Herts, UK. The Ag-NP image from a transmission electron microscopy (TEM, Tec nai G2 20 S-TWIN, FEI, USA) is showed in Fig. 1 that silver nanoparticles are in the size range of 50–100 nm. The suspension of the nano-Ag was prepared in deionized water and dispersed by ultrasonic vibration (KQ2200E, Kunshan, China) for 20 min. This suspension was then stirred on vortex agitator before every use. The particle size of nano-Ag in suspension was characterized by dynamic light scattering (DLS) using a Zeta-PALS + BI-90 Plus (Brookhaven Instruments Corp., USA) at a fixed wave-length of 659 nm and the scattering angle of 90°. The zeta potential of the nanoparticles was measured in the suspension with a combination of laser Doppler velocimetry and phase analysis light scattering (PALS) using Zeta-PALS + BI-90 Plus. This Ag-np surface area was also measured as shown in Table 1 using a BET (Brunauer, Emmett and Teller) method.

2.2. Animals

Adult male specific-pathogen free (SPF) Wistar rats weighing 275 ± 20 g were purchased from the Experimental Animal Center of the Chinese Academy Medical Sciences, and acclimated for a week before starting the experiments. Animals were bred under SPF conditions during the entire experiment. The environmental conditions were under controlled at 22 ± 2°C, and 45–55% relative humidity, with 12:12 h light/dark cycle. Drinking water and conventional diet were provided ad libitum. All experiments were carried out according to the protocols approved by the Committee for Animal Care of Nankai University and in accordance with the practices outlined in the Institutional Animal Care and Use Committee (IACUC).

2.3. Experimental design

Rats were randomly divided into 3 groups (8 rats in each group) including control group, low-dose group (Ag-np 3 mg/kg) and high-dose group (Ag-np 30 mg/kg). The dose levels were selected based on preliminary experiments and the previous study (the 28-day oral toxicity study by Kim et al.). From the first day of the experiment, animals of experimental and control groups were administered with Ag-np suspension nasal drops or the vehicle control (normal saline), once every two days for 14 consecutive days. The administrations were tolerated well and no severe adverse effects were observed during the entire experiments. After the administrations, Morris water maze (MWM) was performed, and then the long-term potentiation (LTP) was recorded. Finally rats were sacrificed, and brains were collected. Four samples of the half brain of each group were prepared for hematoxylin and eosin stain after the paraffin section was ready. For the other half of the brains, the hippocampus was separated, and the amount of ROS was tested with kits.

Table 1
Characterization of Ag nanoparticles: particle size, surface area and zeta potential in suspension.

	Particles size (nm)	Surface area (m^2/g)	Zeta potential
Nano-Ag	244.5	12.3	−42.81

2.4. Morris water maze

After 2-week nasal drop administration of Ag-np, MWM was performed. MWM was an established test of spatial cognition and used widely nowadays (D'Hooge and De Deyn, 2001). This system included a circular tub (height 60 cm, diameter 150 cm) and a device which can capture swimming pathway. The maze was placed in a room with soft lighting to eliminate reflection in the water. Three bottles of ink were added into the water in order to make it dark, and a built-in heater was used to set the water temperature at 23.5 °C. The maze was divided into four quadrants, that is northeast (NE), northwest (NW), southeast (SE) and southwest (SW). A circular platform was placed in the middle of northeast quadrant of the pool and 1.5 cm below the water surface. There are two parts of the test, place navigation test and spatial probe test. In other words, they can be called acquisition phase and test phase. During the former phase, animals received two trials every day, one was carried out at 8:00 am and the other was at 18:00 pm, and this phase lasted for the first 5 days. During every trial, rats were gently put into the water, and they would try their best to find the hidden platform in order to escape from the water. If rats failed to locate the hidden platform within 60 s, the experimenter guided them by hand to the platform, and made them staying on the platform for 10 s (Soderstrom et al., 2009). After 5 consecutive days of training, all the rats received a probe trial. The probe trial lasted for 60 s. During this test the platform was removed from the pool. Owing to the memory of the training phase, rats would spend more time in the quadrant in which the platform had been located before, so the numbers of the platform location and the swimming time percentage during the test were recorded as an estimation of their spatial memory. Data were collected with a top scan system above the pool. Besides all of the data were then automatically scored via the top scan computer software package.

2.5. Electrophysiology recording (long-term potentiation recording)

After MWM test, the LTP recording was carried out. Rats were positioned on a stereotaxic frame (SR-6 N; Narishige, Japan) after anesthetized with urethane (1.2 g/kg, i.p.). Two holes in the skull were drilled to allow the insertion of electrodes into the brain after dissection of the scalp. A concentric bipolar stainless steel stimulating electrode with a tip separation of 0.5 mm was placed into the perforant pathway (PP, coordinate: 8.0 mm posterior to bregma, 4.4 mm lateral to the midline, 2.8–3.8 mm ventral from the cortical surface). A monopolar extracellular stainless steel recording electrode, 0.5 mm in diameter, was inserted into dentate gyrus (DG) region (coordinate: 4.2 mm anterior to bregma, 2.5 mm lateral to the midline, 3.0–3.7 mm ventral from the cortical surface). The positions of the two electrodes were readjusted to get the stable curves. First of all, baseline responses (1/min) were recorded for 20 min followed by the induced theta burst stimulation (TBS), consisting of four theta epochs delivered at 0.1 Hz. Each epoch, in turn, consisted of 20 trains of four pulses (at 200 Hz) delivered at 5 Hz at the same stimulus intensity as the baseline pulse. Theta burst stimulation (TBS) lasted 40 s, totally. The single pulse recording resumed for 60 min following TBS.

2.6. ROS assay in hippocampus

After the LTP recording was finished, the brain of each rat was removed and the hippocampus of one side of the brain (opposite to the LTP recording side) was dissected out and rinsed in 0.1 M phosphate buffer (pH 7.4). After being weighted, the hippocampus was homogenized using a glass homogenizer for 5 min along with ice-cold saline to be 10% (w/v) homogenates. And the homogenate mixture was centrifuged at 3000 rpm at 4 °C for 15 min. The supernatant was collected. Then assay the content of ROS in hippocampus homogenate following the instructions provided by the manufacturer of the kit.

2.7. Histology analysis

After the electrophysiology recording, rats were sacrificed by cervical dislocation, and then the brains of the animals were removed carefully, weighed, and fixed in a 10% formalin solution containing neutral phosphate-buffered saline. After dehydration using graded ethanol and vitrification by dimethylbenzene, the organs were embedded in paraffin to cut into slices, then stained with hematoxylin and eosin, and examined under light microscopy.

2.8. Statistical analysis

All data were presented as mean ± SEM. Two-way repeated-measures of ANOVA were applied for analysis of differences between groups during navigation phase. Independent-samples *t*-test was performed on the data from single day during navigation phase for analysis of differences between groups. Data of spatial probe

and LTP recording were compared using independent-samples *t*-test. Statistical differences were taken when $P < 0.05$. The analyses were performed using SPSS 16.0 software.

3. Results

3.1. Characterization of Ag-np

The morphology of the Ag-np in suspension was detected through TEM (as shown in Fig. 1). The characterization of Ag-np was shown in Table 1. The particle size distribution had a wide range from 32.68 to 380.21 nm due to the aggregation, and the hydrodynamic mean diameter was 244.5 nm by DLS test. The nano-Ag particles had a negative zeta potential in deionized water. The values of zeta potential were −42.81.

3.2. Morris water maze

3.2.1. Effect of Ag-np on place navigation test

The learning curves of MWM are shown in Fig. 2A. As the training days going on, all the rats of three groups showed a progressive improvement in the escape latency. However, there were still some differences between three groups. For example, during the first 3 days of training period, the escape latencies of the control group were significantly lower than those of the Ag-np exposure groups. Meanwhile, the escape latencies were lower in rats of low-dose Ag-np treated group than those of high-dose group from the first day to the third day, but the differences became smaller and smaller. To be brief, in acquisition phase, statistical significances were observed between Ag-np treated group and control groups ($P < 0.01$, repeated-measures ANOVA, Fig. 2A), as well as between high-dose group and low-dose group.

3.2.2. Effect of Ag-np on spatial probe test

In spatial probe test, statistical results revealed that both time percentage in target quadrant and number of platform location crossings had a marked difference between three groups. Compared with the control group, both time percentage (Fig. 2C) and number of platform location crossings (Fig. 2B) in target quadrant were decreased in drug-treated groups than those of control group, and the differences were more obvious in high-dose group.

All of the data above indicated that the space learning-memory ability was weakened in the Ag-np exposure group compared with that of control group. The higher dosage of Ag-np the rats received, the more serious on their impairment was.

3.3. Long-term potentiation

Generally speaking, the long-term potentiation is thought to be the basement of memory. As the MWM data showed impaired learning and memory ability in rats, possibly, there were changes of LTP.

Results of the LTP were showed in Fig. 3. From the curve, we can see that slopes of the field excitatory postsynaptic potentials (fEPSPs) increased immediately after the high frequency stimulation and stabilized to a level above the baseline period. However compared with the control group, it was found that fEPSPs slopes were obviously lower in Ag-np treated groups. Nevertheless, the fEPSPs slopes were lower in high-dose group than those of low-dose group.

3.4. ROS assay in hippocampus homogenate

The concentrations of ROS in hippocampus were measured in these three groups. The result (Fig. 4) indicated that both concentrations of superoxide anion and hydroxy radical in hippocampus were higher in Ag-np treated groups compared with those in control group.

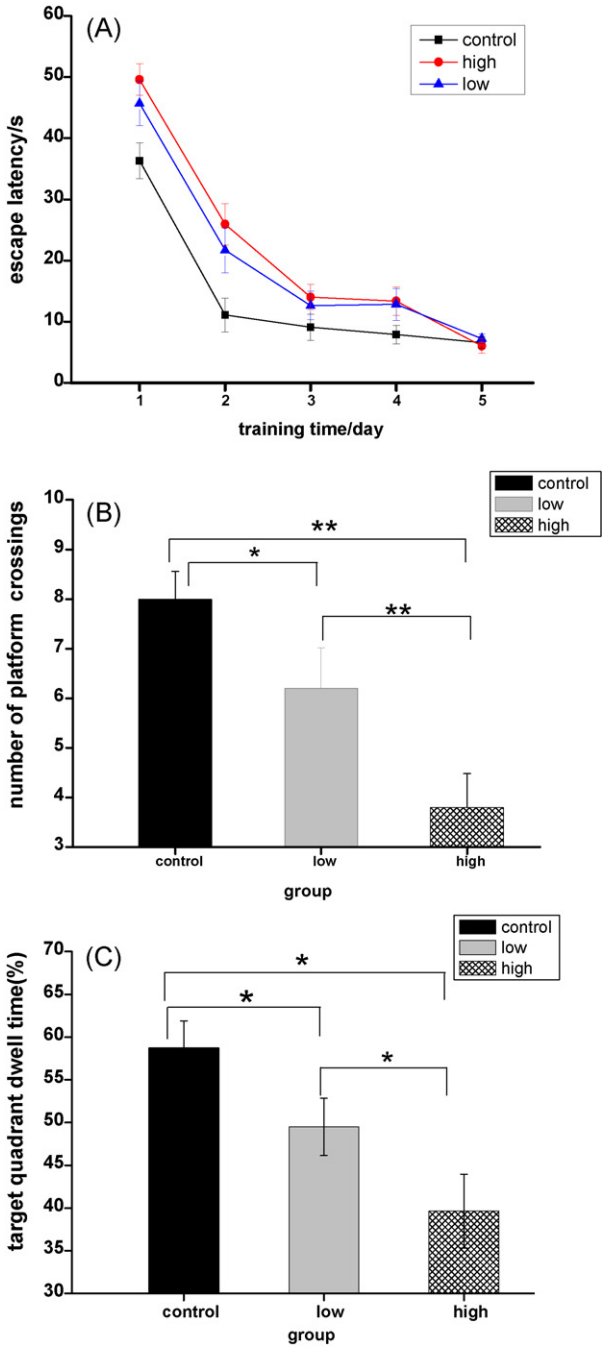

Fig. 2. Rats' performance in MWM test. (A) Mean escape latency calculated for each day in place navigation phase. (B) Mean number of platform area crossings in spatial probe phase. (C) Mean percentage of time in target quadrant in spatial probe phase. Data are expressed as mean ± SEM. No significant, $P > 0.05$; $^{*}P < 0.05$; $^{**}P < 0.01$. $n = 8$ in low dose Ag-np group, high dose Ag-np group and control group.

3.5. HE staining analysis

The HE staining was applied to observe the neuronal injury induced by Ag-np. There was a normal morphology of pyramidal neurons in the PP and DG regions of hippocampus in rats of control group (Fig. 5-Sham). The outline of pyramidal neurons in the PP and DG regions of hippocampus were greatly altered in Ag-np exposure groups compared to those in control group. It can be seen

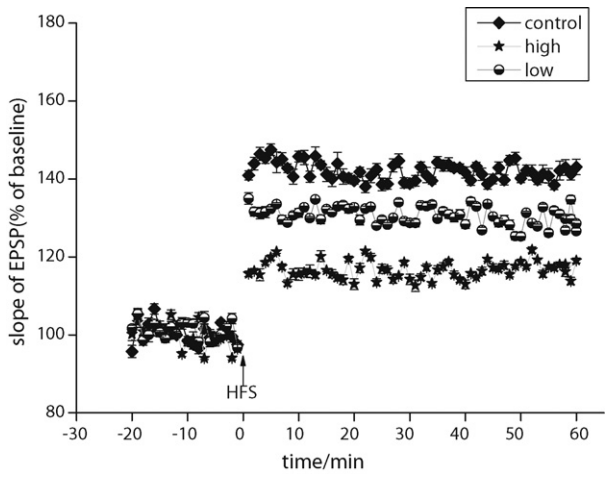

Fig. 3. The effect of Ag-np on LTP from PP to DG area. Changes in fEPSPs slope after HFS. The fEPSPs slope is plotted as a percentage change against the baseline before HFS. Arrow represents application of HFS.

that there was a clear edema and nuclear shrink phenomenon as well as neorobiosis among the neurons (Fig. 5).

4. Discussion

As having the broad-spectrum antimicrobial properties, silver is used in a lot of aspects, and along with the rapid development of nanotechnology, applications of Ag-np have been extended further and now nano-silver is one of the most commonly engineered nanomaterials used in consumer products (Rejeski, 2009). Exposure to nano-silver is becoming increasingly widespread and intimate. On the other hand, nanoparticle-induced drug delivery to the brain may impose risks to patients (Muthu and Singh, 2009; Yang et al., 2010). So it is necessary to investigate the effects of silver nanoparticles on nervous system. In this research it was focused on whether the presence (or even accumulation) of Ag-np in the brain had some effects on the hippocampal synaptic plasticity and spatial cognition.

In this study, rats were exposed to Ag-np by nasal drops administration. Because of the small size, the nanoparticles are expected to get across the blood–brain barrier (BBB) by either passive diffusion or by carrier-mediated endocytosis (Hoet et al., 2004). At the same time, nanoparticles may be taken up directly into the brain by transsynaptic transport (Oberdorster et al., 2004). Tang et al. examined the distribution and toxicity of nano-silver in rats following subcutaneous injection. They found that this particle was translocated to the circulation and finally distributed to the brain and some other target organs that included kidneys, livers and lungs. Because Ag-np can induce blood–brain barrier destruction, it can easily make its way to the brain (Tang et al., 2009). Besides, a research of Panyala also found that silver can enter through the BBB and accumulate in different brain regions (Rungby and Danscher, 1983).

The MWM test has been widely used as an effective behavioral tool for examining learning and memory in animals (D'Hooge and De Deyn, 2001). From the data it was showed that rats administered with Ag-np had a worse performance compared with those of control. In this study, the place navigation phase, escape latency and swimming speed were examined. Data of MWM showed that the escape latencies were prolonged in two Ag-np administered groups, and more significant in high-dose group, which suggested that the rat's learning ability was impaired because of the exposure to silver nanoparticles. At the same time, during spatial probe test, both the quadrant dwell time and platform crossings were decreased in the Ag-np administered groups, which indicated that the rats' spatial memory were obstructed after Ag-np exposure. The above data means that both the learning ability and retention

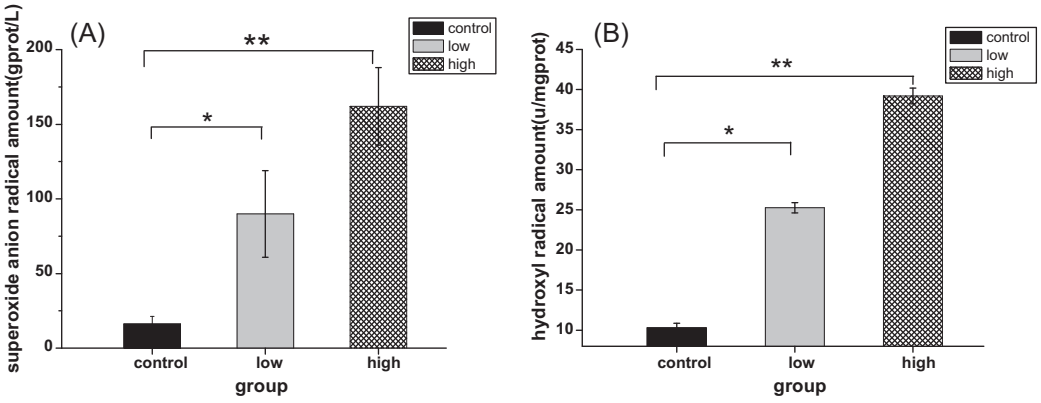

Fig. 4. ROS content in the hippocampus. (A) Superoxide anion content; (B) hydroxy radical content. Data are presented as mean ± SEM (*$P < 0.05$).

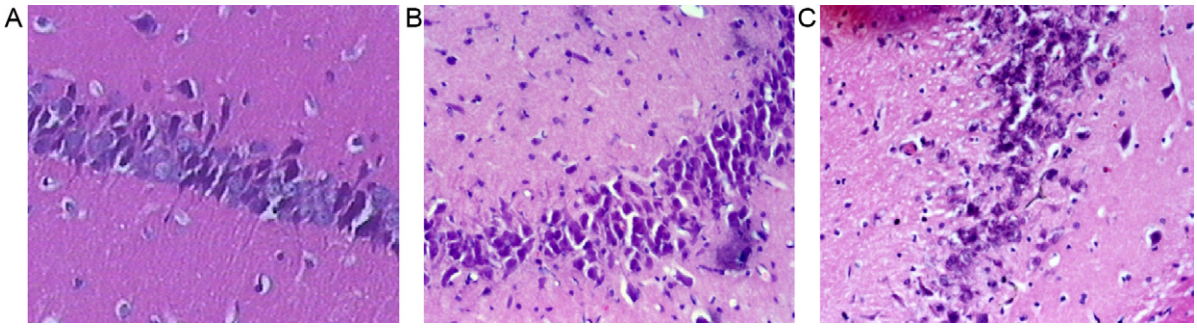

Fig. 5. Histological findings in hippocampus: (A) control group, (B) low-dose group, and (C) high-dose group.

of memory were damaged after exposure of Ag-np, and the severity of impairment was associated with the dosage of Ag-np.

LTP in hippocampus was an important functional index on the potency of synaptic connections, and it can help to understand how memories were formed at the cellular level (Malenka and Nicoll, 1999). From the result of the MWM test it was found that rats of two groups had a cognitive deficits after exposure to Ag-np. Meanwhile, the LTP from PP to DG region was recorded with measuring the fEPSPs slope. The decreased fEPSPs slope in Ag-np administered groups was consistent with the impaired LTP, which may account for their poor performance in the MWM test.

The HE staining slice showed that there was a clear edema and nuclear shrink phenomenon as well as neorobiosis among the neurons in regions of hippocampus. As we know that one neuron can be connected to a lot of other neurons by either dendrites or axons, but with so many neuron apoptosis, the connection would be weakened tremendously, and this may be account for the impairment of LTP. Rahman et al. evaluated the toxicity of Ag-np in mouse brain after intraperitoneal injection. Results showed that Ag-np produced apoptosis and neurotoxicity via ROS and some other factors (Rahman et al., 2009). ROS includes hydroxy radical, superoxide anion and so on. It is generated during many life activities. Generally speaking, there are some anti-oxidant defense mechanisms in organism, to keep a balance of redox equilibrium. However once the generation of ROS exceed the capacity of the anti-oxidant defense mechanism, oxidative stress occurs. So we tested the content of hydroxy radical and superoxide anion in hippocampus homogenate. The result showed that both of them were raised obviously compared with those of control group (Fig. 4). That may confirm that Ag-np produced neurotoxicity via ROS. Furthermore oxidative stress can elicit a wide variety of pathological and cellular events including stress, inflammation, DNA damage and apoptosis (Ryter et al., 2007; Ahamed et al., 2010). A lot of researchers reported that Ag-np induced cytotoxicity, DNA damage and apoptosis via membrane lipid peroxidation, ROS and oxidative stress (Foldbjerg et al., 2009; Park et al., 2010). Among all kinds of organelles, mitochondria appear to be sensitive target for Ag-np toxicity. Asharani et al. suggested that Ag-np can induce disruption of the mitochondrial respiratory chain, therefore increased ROS production and interruption of ATP synthesis, and finally leading to DNA damage (AshaRani et al., 2008). Hsin et al. demonstrated involvement of the mitochondria-dependent jun-N terminal kinase (JNK) pathway in Ag-np induced apoptosis (Hsin et al., 2008).

5. Conclusion

The nasal administration of Ag-np induced learning and memory deficits in rats was observed, as represented in MWM performance. The mechanisms of Ag-np neurotoxicity, at least partly, lay in the impairments of synaptic plasticity. From the result of LTP, it can be clearly seen that Ag-np attenuated LTP in the PP to DG regions of hippocampus, and then the learning and memory impairment emerged. The ROS assay in hippocampus homogenate suggested that the over-generation of ROS may lead to an oxidative damage, including stress, inflammation, DNA damage and apoptosis, as showed by the HE staining slice. Although Ag-np attributed to induce impairment of hippocampus function in rats, the differences between human beings and rodents in metabolism, their toxicity dosage level and sensitivity threshold are still needed to be rigorously investigated. Moreover, for a better understanding of Ag-np neurotoxicity, further studies on the essential mechanisms underlying the development of cognitive deficits induced by Ag-np would be absolutely necessary.

Conflict of interest

None.

Acknowledgments

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