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ROS-Drp1-mediated mitochondria fission contributes to hippocampal HT22 cell apoptosis induced by silver nanoparticles

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ABSTRACT

Silver nanoparticles (AgNPs) have widely used in industrial and medical applications for their excellent antibacterial activities. AgNPs can penetrate into the brain and cause neuronal death, but limited evidence focused on toxic effects and mechanic study in hippocampal neuron. This study aimed to investigate the molecular mechanisms of mitochondrial damage and apoptosis in mouse hippocampal HT22 cells and further to explore role of reactive oxygen species (ROS) and GTPase dynamin-related protein 1 (Drp1) in AgNPs-induced neurotoxicity. Our results showed that acute exposure to AgNPs at low doses (2–8 μg/mL) increased ROS generation, decreased mitochondrial membrane potential (MMP) and ATP synthesis in HT22 cells. In addition, AgNPs promoted mitochondrial fragmentation and mitochondria-dependent apoptosis via excessive mitochondrial fission/fusion by 8 μg/mL AgNPs treatment for 24 h. The mechanism was involved in increased protein expression of Drp1, mitochondrial fission protein 1 (Fis1), mitofusin 1/2 (Mfn1/2) and inhibited optic atrophy 1 (OPA1), and mainly mediated by phosphorylation of Drp1 Ser616. The AgNPs-induced mitochondrial impairment and apoptosis was mainly due to their particle-specific effect rather than silver ions release. Furthermore Drp1-mediated mitochondrial fission contributed to mitochondria-dependent apoptosis induced by AgNPs, all aforementioned changes were significantly rescued by N-acetyl-L-cysteine (NAC) and Mdivi-1 except for OPA1 protein expression. Hence, our results provide a novel neurotoxic mechanism to AgNPs-induced neurotoxicity and revealed that the mechanism of mitochondria-dependent apoptosis in HT22 cells was mediated by excessive activation of ROS-Drp1-mitochondrial fission axis. These findings can deepen current evidences on neurotoxicological evaluation of AgNPs and aid in guiding their proper applications in different areas, especially in biomedical use.

1. Introduction

Silver nanoparticles (AgNPs) exhibit distinctive physical, chemical and biological properties that make them suitable for disease therapeutics, medical imaging and molecular diagnostics [1]. For these applications, AgNPs unavoidably enter the human body distribute in the central nervous system (CNS), leading to neurotoxicity and consequently threatening human health [2]. Despite numerous publications on the neurotoxicity of various AgNPs *in vitro* and *in vivo* [2,3], details of AgNP-induced neurotoxicity need to be elucidated. Mitochondria are major target of AgNPs-induced cytotoxicity [4]. The involved changes included mitochondrial membrane potential (MMP) loss, oxidative phosphorylation inhibition, calcium dynamics disruption and reactive oxygen species (ROS) elevation, eventually caused mitochondria-dependent apoptosis [4,5]. AgNPs were reported to induce apoptosis in HT22 cells, which is mitochondria-dependent [6]. But involved molecular mechanisms targeting mitochondria remain unclear in the AgNPs-induced neurotoxicity. As hippocampal neuron was vulnerable to AgNPs, more neurotoxic effects should be deeply understood.

Mitochondrial fission/fusion are the process that mitochondria undergo coordinated dynamic cycles. The events refer to mitochondria dynamics that closely related with mitochondrial function to maintain energy metabolism, calcium homeostasis and redox balance and cell fate [7]. Mitofusin 1 (Mfn1), Mitofusin 1 (Mfn2) and optic atrophy 1 (OPA1) are fusion proteins that control mitochondrial fusion. Fission is orchestrated by mitochondrial fission protein 1 (Fis1), which recruits cytosolic GTPase dynamin-related protein 1 (Drp1) to cleave mitochondria [8].

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