Nanoceria and Its Biomedical Relevance

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Abstract

Nanoceria is a nanosized particle preparation of cerium oxide. It shows mixture of cerium in the 3+ and 4+ states on the nanoparticle surface, giving it interesting redox properties. Nanoceria shows effective biological antioxidant properties, which makes it a great candidate for biomedical applications. Many studies have shown promising results on therapeutic potential of nanoceria in diseases like cancer, diabetes, atherosclerosis, and neurodegenerative diseases. Meanwhile, other studies explored biodistribution and toxicity of nanoceria. This review article describes nanoceria, its relevant biomedical applications, and adverse effects, based on previously reported studies.

Keywords

- cerium oxide nanoparticles
- antioxidant
- reactive oxygen species
- inflammatory diseases

Introduction

Cerium is a rare earth metal having atomic number 58, belonging to lanthanide series. Unlike most rare earth metals, cerium can exist in both 3+ and 4+ states and thus, oxides of cerium exist as both CeO_2 and Ce_2O.[1,2] Cerium oxide nanoparticles (nanoceria) show mixture of erium in the 3+ and 4+ states on their surface, giving them interesting redox properties. Nanoceria is being widely used in fields of chemicals, cosmetics, mechanical polishing/planarization, corrosion protection, solar cells, fuel oxidation catalysis, and automotive exhaust treatment.[1,2] Other than these applications, nanoceria also displays many biorelevant activities—mimicking superoxide dismutase (SOD), catalase, peroxidase, oxidase, and phosphatase, and scavenging hydroxyl radicals, nitric oxide radicals, and peroxynitrite.[1] These biorelevant activities of nanoceria can be used in pharmacological agents, drug delivery, and bioscaffolding.[1]

Synthesis of Nanoceria

Numerous techniques, such as green synthesis, hydrothermal, solvothermal, aqueous precipitation, reversed micelles, thermal decomposition, and flame spray methods have been reported to synthesize nanoceria, while maintaining control of its size and properties.[1-3] The synthesized nanoceria can be bare or wrapped with a coating of protective substances that can be hydrophilic or hydrophobic.[3] Naked nanoceria has poor water solubility, and thus limited biological applications. Polymer coating of nanoceria enhances its stability, biocompatibility, and water solubility.[2] For biological use, biocompatible nanoceria has been systematically synthesized in pure water or with coating/functionalization of polyethylene glycol, dextran, polyacrylic acid, cyclodextrin, glucose, and so on.[3,4] Methods of nanoceria preparation or synthesis are important because they determine the solubility, size, surface condition, charge, structural arrangement, and morphology of nanoparticles, thus affecting their properties, including catalytic activities.[3]

Mechanism of Action

The basis for activities of nanoceria is the thermodynamic efficiency of redox-cycling between 3+ and 4+ states on their surface and their unique ability to take up and release oxygen.[1] Nanoceria could have a dual role as an oxidation catalyst and reduction catalyst, depending on the reaction conditions and surrounding microenvironment. The cerium atom on surface of nanoceria has the ability to easily and drastically adjust its electronic configuration to fit its immediate environment, and thus contributing to redox and antioxidant properties.[3] The Ce^{3+}/Ce^{4+} valence switching capacity of nanoceria makes it an SOD mimic.[3] Nanoceria could also act as catalase mimic in a redox-state-dependent manner, and higher levels of cerium in the +4 state exhibit higher activity.[3] Nanoceria can also show pro-oxidant properties at lower pH and high concentrations, and it has shown potential toxicity based on synthesis method, concentration, and exposure time.[5]

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Biomedical Applications

Increased oxidative stress has been found to be associated with many neurodegenerative and chronic inflammatory diseases like Alzheimer's, Parkinsonism, Rheumatoid Arthritis (RA), Ischemic stroke, and diabetes etc. Due to its antioxidant properties, nanoceria has been studied extensively for treatment of these disorders.[3,6] Nanoceria shows neuroprotective effects by protecting against free radical/ reactive oxygen species (ROS) mediated injuries. Nanoceria administration in rat model of Parkinsonism (6-OHDA-induced) resulted in partial neuroprotection against disturbances in motor performance, partially through their antioxidant and antiapoptotic effects.[7] Many studies have also confirmed antibacterial activity of nanoceria against Pseudomonas aeruginosa, E. coli, B. subtilis, Shewanella oneidensis and Pseudokirchneriella supcapitata.[2]

Diabetes is also believed to be associated with oxidative stress and beneficial effects of nanoceria have been demonstrated in diabetic rats.[8] In another study, nanoceria treatment significantly reduced glucose levels and diabetogenesis in streptozocin induced diabetic Swiss mice. In addition, cytokines (IL-6 and TNF-α and p65-NF-κB) expression were diminished by nanoceria treatment, whereas the nuclear factor erythroid 2-related factor 2 (Nrf2) expression was enhanced, indicating the role of modulation of NF-κB/Nrf2 pathway. Nanoceria also exhibited promising superoxide dismutase 1 mimetic and antiapoptotic activity in these diabetic mice.[9]

Nanoceria has also been shown to reduce retinal degeneration by reducing ROS generation in rat retinal cells.[10] The alginate-gelatin injectable hydrogel loaded with oligo-chitosan coated nanoceria showed good biocompatibility and high potential in protecting cells from apoptosis, angiogenesis, and production of proin£ammatory cytokines in age related macular degeneration cellular models.[11]

Increased ROS production in synovium causes chronic inflammation and contributes to rheumatoid arthritis. Nanoceria and manganese ferrite nanoparticles anchored to mesoporus silica nanoparticles showed synergistic effects by scavenging ROS and promoting recruitment of anti-inflammatory macrophages in joints of rat RA model.[12] Nanoceria also showed therapeutic potential by preventing valvular calcification mediated by ROS related damage,[13] cardio-protective effects by preventing myocardial remodelling,[14] and attenuating ischemia reperfusion induced hepatic injury in rats.[15]

Antioxidant and anti-inflammatory properties of nanoceria were found beneficial in cisplatin induced nephrotoxicity. As nanoceria ameliorated oxidative stress by showing a reduction in levels of malondialdehyde, increased levels of endogenous antioxidants, reduced glutathione and catalase, and decreased levels of proinflammatory cytokines.[16] In vivo studies in mice with induced liver toxicity (by carbon tetrachloride [CCl4]) showed that nanoceria administered mice exhibit findings similar to mice treated with N-acetyl cystine (NAC), a common therapeutic to reduce oxidative stress.[17]

Nanoceria has also shown potential for treatment of smoking-related diseases by exhibiting ability to protect against cigarette smoke extract (CSE)-induced oxidative stress and inflammation in cultured rat H9c2 cardiomyocytes. Results indicated that nanoceria can inhibit CSE-induced cell damage via inhibition of ROS generation, NF-αB activation, inflammatory gene expression, and antioxidant depletion.[18] Another study showed anti-inflammatory and antioxidant effects of nanoceria in both healthy rats, and rats with pneumonia.[19]

Many studies have shown that nanoceria is toxic to cancer cells.[3] Nanoceria induces ROS mediated damage, lipid peroxidation, apoptosis, and membrane leakage in cancer cells, but not in healthy/normal cells.[3] This has been attributed to cancer cells having a more acidic cytosolic pH than normal cells because of higher glycolysis and lactate production.[3] Although, results from few studies are conflicting. Nanoceria treatment to human monocytic leukemia cells (THP-1) resulted in reduction of ROS but cytotoxicity was not observed.[20] A study in broncho-alveolar carcinoma-derived A549 cells showed that uptake of the nanoceria resulted in slight change of the cell cycles, i.e., more cells stayed in the G1 phase but the cell viability was not significantly altered.[21]

When functionalized with anticancer molecules, nanoceria demonstrate synergistic toxic effects in cancer cells.[3,22,23] Protective effects of nanoceria on healthy cells, while killing glioma cancer cells have been reported.[24] Nanoceria abolished toxic effects of anticancer drug (doxorubicin) on human dermal fibroblasts.[25]

The multi-enzyme-like properties of nanoceria have been successfully used for biological detection and analysis, e.g., colorimetric immunoassays, enzyme-linked immunosorbent assay (ELISA), and biosensors etc.[3,26-28]

Biodistribution

In vivo analysis of the biological distribution of nanoceria administered to mice perorally (PO), intravenously (IV), or intraperitoneally (IP) showed that the IV and IP administration leads to most extensive and cumulative nano-deposition while PO administration led to excretion of greater than 95% nanoceria within 24 hours. Organ deposition for IV and IP mice was highest in the spleen followed by the liver, lungs, and kidneys. Nanoceria was excreted through feces all administration routes.[17] Study in C. elegans showed that positively charged nanoceria is significantly more toxic and accumulated to a greater extent than the neutral and negatively charged nanoceria.[29]

Toxicity and Adverse Effects

Cerium is not found in the human body and there are no known clearance mechanisms for it. This implies that exposure to cerium would lead to systemic toxicity.[1] Nanoceria is successfully up taken by cells in both normal and diseased states through multiple routes. In most cases of in vitro intracellular assays, nanoceria was reported to exhibit positive effects (such as scavenging ROS) and was regarded as a promising biomaterial for biomedical applications. However, several reports suggested that the uptake of nanoceria could induce oxidative stress and DNA damage, apoptosis, dephosphorylation of various substrates, aberrant cell signaling, and alterations in the transcriptional and posttranslational levels.[3,30-32]

In vivo analyses of the biological effect of different sizes of nanoceria have been performed by per-oral, intravenous or intraperitoneal administration to laboratory animals.[3,33] There are few studies showing that exposure of animals to nanoceria resulted in significant lung responses, including lung inflammation, cytotoxicity, lung injury, alveolar macrophage functional changes, induction of phospholipidosis, and release of proinflammatory and fibrotic cytokines. Cerium is also linked to fibrosis of the heart, and nanoceria was shown to induce myocardial fibroblast proliferation and collagen deposition in rats.

Due to the extensive use, nanoceria is getting released to the environment and humans are getting exposed, mostly via inhalation.[2] Nanoceria is used as a diesel fuel catalyst, and thus can be emitted into air, resulting in exposure to humans by inhalation. A recent study investigated the acute (24 hours) effect of intratracheal (IT) instillation of nanoceria on pulmonary and systemic inflammation, oxidative stress and thrombosis in mice. Results showed that acute pulmonary exposure to nanoceria induced pulmonary and systemic inflammation, oxidative stress, and thrombosis in vivo.[34] Nanoceria administration has shown to result in elevated WBC counts after IV and IP administration in mice,[17] and hepatic injury with oxidative stress in rats after single vascular infusion.[35]

Above data necessitates careful optimization of applications and synthesis parameters to generate nontoxic nanoceria that are based on the treatment strategy being used, and further exploration of biochemical effects of nanoceria.[1,3]

Conflict of Interest

None declared.

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