Review Article

Dual Role of Nano Ceria- as an Antioxidant and as a Prooxidant

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Abstract

Metal oxide nanoparticles are profoundly used in different fields of biological applications as well as in physics due to their unique characteristics of semiconducting nature at nano size. The surface to volume ratio increases enormously thereby making these metal oxide nanoparticles physicochemically different from their bulk counterpart. In this book chapter we will discuss about cerium oxide nanoparticles (CeO-NPs) and its different valance states which enables it to act both as a prooxidant as well as an antioxidant. CeO-NPs are used in different products like catalyst in solar cells, sensors and catalyst for detection of certain gases, as antioxidant, in biomedical field etc. Due to its profound applications the toxicity exerted by these CeO-NPs needs to be explored. There are conflicting evidences regarding the toxicity of CeO-NPs as found from previous literatures. In some cases, it is known as a reactive oxygen species (ROS) scavenger whereas in some it is known to exert oxidative stress. This dual nature is attributed to the coexistence of its two valance states Ce⁺³ and Ce⁺⁴. Thus, the transition between these two states play an important role in deciding whether CeO-NPs is an oxidant or an antioxidant and how it mimics the different antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT). These topics will be discussed elaborately in this review.

Key words : nanoceria, antioxidant properties, nanoceria as prooxidant, ROS scavenging, cerium oxide stoichiometry

Introduction

In many fields of chemistry, physics and materials science, metal oxides are widely used.¹⁻⁶ Metal oxide nanoparticles can be found in several geometrical structures such as tubes, spheres, prisms, flowers and rods having electronic structure that enables them to have metallic, semiconductor or insulating character. The band gap of the nanoparticles enables them to possess a semiconducting nature. Cerium oxide nanoparticles (CeO-NPs) are one of the metal oxide nanoparticles which have excellent catalytic activities that are derived from Ce⁴⁺ and

Ce³⁺ oxidation state. The electronic configuration of cerium atom has the ability to easily and drastically adjust to its environment. It arises through loss of oxygen and/or its electrons, alternating between CeO₂ and CeO_{2-x} during redox reactions and also exhibits oxygen vacancies, or defects, in the lattice structure. CeO-NPs are recently found to mimic the multi-enzyme activities like superoxide dismutase (SOD) and catalase (CAT). In biological fields such as biology, medicine, bioanalysis, biomedicine, drug delivery, and bioscaffolding, CeO-NPs has emerged as an effective nanomaterial.^{7, 8} The existence of

cerium is as a rare earth metal of the Lanthanide series which has an atomic number of 5.⁸ It is well known that the metals in rare earth series exist mostly in trivalent state, however cerium is an exception. The electronic configuration of cerium ($[\text{Xe}]_4f^1d^1s^2$) can display both the trivalent (+3) ($\text{Ce}^{3+} = [\text{Xe}]_4f_1$) and tetravalent (+4) ($\text{Ce}^{4+} = [\text{Xe}]$) oxidation states.^{9,10} Due to the antiemetic, bacteriostatic, bactericidal, immunomodulating and antitumor activity, Ce^{3+} salts (nitrate, acetate, chloride, etc.) have been traditionally used by humans for biomedical purposes.^{11,12} The capacity to actively scavenge a variety of both reactive oxygen species (ROS) and reactive nitrogen species (RNS) in cell and animal models demonstrated antioxidant enzyme-mimetic activity of CeO-NPs. In current scenario, as catalysts and as structural and electronic promoters of heterogeneous catalytic reactions, CeO-NP and CeO-NP-containing materials have come under intense scrutiny.¹³ Since, the Ce atom exists in both trivalent (Ce^{3+}) and more stable tetravalent (Ce^{4+}) state, it allows the nanoparticles to store and release oxygen when present in the form of CeO_2 .¹⁴ To increase its catalytic properties in industry, it is desirable to produce CeO_2 with increased oxygen storage and releasing properties.

Stoichiometric state of Ce^{3+} and Ce^{4+}

To a certain extent, both the enzyme-mimetic and ROS/RNS scavenging capacity of CeO-NPs is dependent on the physicochemical properties of the nanoscale materials and the thermodynamic efficiency of redox cycling between Ce^{3+} and Ce^{4+} ions on the surface of CeO-NPs.^{10,15} Cerium oxide can exist as pure CeO_2 (Ce^{4+}) or Ce_2O_3 (Ce^{3+}) in bulk scale and compared to bulk scale, the surface of CeO-NP contains a mixture of both Ce^{4+} and Ce^{3+} .^{16,17} The absolute diameter of the CeO-NP decreases (e.g., from 20 nm to 2 nm) when there is a loss of oxygen atom and there is an increase in the Ce^{3+} ions on the surface of the nanoparticles.¹⁸⁻²⁰ When Ce^{4+} is converted to Ce^{3+} thereby changing the oxidation state of Ce, the number of vacancies for oxygen are increased on the surface of CeO-NP, as oxygen is lost from the surface. The antioxidant/enzyme-mimetic activity of the CeO-NPs is directly proportional to the ratio of $\text{Ce}^{3+}/\text{Ce}^{4+}$ sites available on the surface of the nanoparticle. Each oxygen vacancy is created by the reduction of two surface Ce^{4+} ions to maintain the stability of electronic charge. Thus, the oxygen vacancy present under these conditions can be illustrated using the formula CeO_{2-x} showing the structural stability of CeO-NPs.¹⁸ Studies have found a dual nature of CeO-NPs either it exhibits toxicity mediated by production of ROS^{21,22} or by acting as an antioxidant.²³ To generate superoxide anions, the reduction of Ce^{4+} to Ce^{3+} can produce damaging hydroxyl radicals. Ce^{3+} acts as an antioxidant when it reacts with hydroxyl radicals.^{10,22,24,25}

Thus, it has been found that the valence state of Ce decides whether CeO-NPs will play a protective or toxic role when exposed to cells. If the ratio of $3+/4+$ is higher, CeO-NPs will have increased toxicity and decreased antioxidant potential.

In vitro and in vivo studies on nanoceria exposure

Through multiple routes both normal and diseased states of mammalian cells was successfully up taken by CeO-NP.²⁶ CeO-NP exhibits positive effects (such as scavenging ROS) and was used as a promising biomaterial for biomedical applications in most cases of in vitro intracellular assays,⁷ dephosphorylation of various substrates, aberrant cell signalling and alterations in the transcriptional and posttranslational levels, CeO-NP could induce oxidative stress and DNA damage.^{22,27,28} Through autophagy and a mitochondrial apoptosis pathway CeO-NP could induce cytotoxicity.²⁷ The cytotoxicity of CeO-NP with cell types or particle size/preparations of simple correlations has not been established.²⁹

Peroral, intravenous or intraperitoneal administrations of CeO-NPs to laboratory animals were used for studying the in vivo activity of these nanoparticles. The degeneration of retina induced by intracellular peroxides could be prevented by CeO-NP.³⁰ Animal models for the diseases like ischemic stroke,³¹ lupus,³² diabetes,³³ radiation-induced pneumonitis,³⁴ and ischemic cardiomyopathy³⁵ could be found to be prevented by CeO-NPs administration. The effect can be attributed due to the ROS scavenging ability of CeO-NPs. CeO-NP resulted in significant lung responses, including lung inflammation, lung injury, cytotoxicity, induction of phospholipidosis, alveolar macrophage functional changes, and release of pro-inflammatory and fibrotic cytokines when, exposed to animals.³⁶ CeO-NP was shown to induce myocardial fibroblast proliferation, collagen deposition in rats related to fibrosis of the heart.³⁷ Since cerium is not found in humans, systemic toxicity may be found as there is no clearance mechanism for this metal.

Reactive oxygen species (ROS) and ROS scavenging mechanism

Free radicals, such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), and peroxynitrite (ONOO^-) are highly reactive metabolites of oxygen known as reactive oxygen species (ROS). The generation of ROS is depicted using band gap diagram is shown in Fig. 1.

In the intracellular and extracellular environment, antioxidants exist both in enzymatic and non-enzymatic forms. In different pathophysiological conditions ROS and RNS are responsible for the

oxidative stress.³⁸ By enhancing cellular defenses in the form of antioxidant, the oxidative stress can be effectively neutralized.^{39, 40} Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSHPx) are protective enzymes that increases the level of endogenous antioxidants and scavenges free radicals.⁴¹ Based on their activity, antioxidants can be categorized as enzymatic and nonenzymatic antioxidants. Breakdown and removing the free radicals are executed by the enzymatic antioxidants. In a multi-step process, in the presence of cofactors such as zinc, copper, iron, and manganese, the antioxidant enzymes convert harmful oxidative products to hydrogen peroxide (H_2O_2) and then to water. Interrupting the free radical chain reactions are executed by the non-enzymatic antioxidants. Carotenoids, vitamin C, plant polyphenol, vitamin E, and glutathione are the few examples of the non-enzymatic antioxidants.⁴² The inducers and scavengers of ROS are shown in Fig.2.

Inside the cells, there is a cellular imbalance between endogenous antioxidant defences (free radical scavenging by small molecule antioxidants and/or redox enzymes) and ROS generation (e.g., superoxide radical anion ($O_2^{\bullet-}$); hydrogen peroxide (H_2O_2); hydroxyl radical ($\bullet OH$)). This imbalance is one of its

primary characteristics of oxidative stress which causes many serious diseases. As a result of normal cellular metabolism, the production of $O_2^{\bullet-}$ acts as a signalling molecule in the cellular environment. Activation of NADPH oxidases during inflammatory responses and/or disruption of the mitochondrial electron transport chain and interference with ATP production $O_2^{\bullet-}$ levels can rise quickly. Through the activity of superoxide dismutase (SOD) enzymes⁴³ located extracellularly and in the cytoplasm and mitochondria, the toxic effects from excess $O_2^{\bullet-}$ are normally controlled and reduced. By converting $O_2^{\bullet-}$ into H_2O_2 and O_2 through a two-step, catalytic dismutation reaction and thus, SOD enzyme eradicates $O_2^{\bullet-}$.⁴⁴

(1) $O_2^{\bullet-} + 2H^+ + (Cu^+)-SOD \rightarrow H_2O_2 + (Cu^{2+})-SOD$
 (2) $O_2^{\bullet-} + (Cu^{2+})-SOD \rightarrow O_2 + (Cu^+)-SOD$
 (3) $2O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2$ (overall)
 H_2O_2 is finally reduced to water by the enzyme catalase (CAT).

The removal or addition of electrons to $O_2^{\bullet-}$ is done by SOD enzyme. The above reactions explain the scavenging effect by the antioxidant enzymes. In step (1), the removal of an electron from $O_2^{\bullet-}$ to generate H_2O_2 is followed by the reduction of $(Cu^+)-SOD$. On the other hand in step (2), the addition of an electron to another molecule of $O_2^{\bullet-}$ to generate O_2 , is followed by the oxidation of $(Cu^{2+})-SOD$, (which is generated in step (1)). To start the cycle again, reduction of $(Cu^+)-SOD$ is regenerated. To produce every molecule of H_2O_2 , all two $O_2^{\bullet-}$ molecules are dismutated. Similarly, as reported above the presumed catalytic mechanism occurs through scavenging of $O_2^{\bullet-}$ by CeO-NPs.^{30, 56}

(4) $O_2^{\bullet-} + Ce^{3+} + 2H^+ \rightarrow H_2O_2 + Ce^{4+}$ (Ce^{3+} is oxidized)
 (5) $O_2^{\bullet-} + Ce^{4+} \rightarrow O_2 + Ce^{3+}$ (Ce^{4+} is reduced)

The ROS generated in our body has dual effect based on the amount generated which is shown in Fig. 3.

In the actual biological environment these reactions are illustrated by the regenerative capacity of the Ce^{3+}/Ce^{4+} redox couple, and it was previously not clear that these are the identical SOD-mimetic reactions that occur with CeO-NPs. The first investigators to demonstrate the SOD-mimetic activity of CeO-NPs were Korsvik et al.¹⁰. To be more efficient scavengers of $O_2^{\bullet-}$, CeO-NPs were prepared with lower Ce^{3+}/Ce^{4+} ratios on the surface and were compared with CeO-NPs having a high Ce^{3+}/Ce^{4+} ratio (higher levels of Ce^{3+} on the surface). The study revealed that CeO-NPs with low Ce^{3+}/Ce^{4+} surface ratios (higher proportion of surface Ce^{4+}

Figure 3: The dual role of ROS level in our body

ions) were not effective SOD-mimetics as compared to the CeO-NPs having a higher $\text{Ce}^{3+}/\text{Ce}^{4+}$ surface ratio.⁴⁵

Antioxidant ROS/RNS scavenging activity of ceria nanoparticles

The effective reduction in $\text{O}_2^{\bullet-}$ and H_2O_2 levels using CeO-NPs have been demonstrated through their antioxidant SOD- and CAT-mimetic activity. The CeO-NPs have been however, found to be efficient scavengers for other ROS such as $\text{OH}^{\bullet}$.^{25, 46-48} and also for RNS such as nitric oxide radical ($\text{NO}^{\bullet}$)^{49, 50} and peroxynitrite (O_2NO^-).⁵¹ CeO-NPs possess innate $\text{OH}^{\bullet}$ scavenging potential from H_2O_2 which was also indirectly suggested.²⁵ Further, Xue et al., showed that CeO-NPs can efficiently scavenge $\text{OH}^{\bullet}$ based on NP size and Ce^{3+} surface levels. CeO-NPs can prevent the reduction of absorbance of the dye methyl violet with efficient $\text{OH}^{\bullet}$ scavenging. The scavenging was efficient and as size of the CeO-NPs decreased and as the level of Ce^{3+} on the surface of the NPs increased (higher $\text{Ce}^{3+}/\text{Ce}^{4+}$ surface ratios). Switch from Ce^{3+} to Ce^{4+} is a key factor for their ROS scavenging activity and it was the reversible ability of CeO-NPs. There are two step mechanism for the $\text{OH}^{\bullet}$ scavenging activity of CeO-NPs, where the oxidation of Ce^{3+} by $\text{OH}^{\bullet}$ indicates the first step and the reduction of Ce^{4+} to regenerate Ce^{3+} indicates the second step.⁴⁷

Discussion and Conclusion

Reactive oxygen species (ROS) are highly reactive metabolites of oxygen, such as superoxide ($\text{O}_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and peroxynitrite (ONOO^-). Their lifetime in biological systems ranges from nanoseconds to seconds depending on their reactivity and the level of cellular antioxidants.

ROS can exist in both +3 and +4 oxidation state. Although the effect of chronic low dose exposure to oxidant in mammalian cells changes its sensitivity to higher doses of oxidants.^{52, 53} Nanoceria or cerium oxide nanostructure (cluster, particles etc.) are metal oxide semiconductors that have profound applications due to their unique characteristics like high chemical and thermal stability, oxygen storage capability, redox nature and other physicochemical properties which are size tunable.⁵⁴⁻⁵⁷ The nanoceria has a face centered cubic fluorite structure with $\text{Fm}\bar{3}\text{m}$ crystal structure. In this structure the Ce^{4+} cations are placed in the corner of the cubes that are coordinated to the O^{2-} ions which are present in the tetrahedral voids.⁵⁸ Apart from Ce^{4+} , the ions of cerium can also exist in Ce^{3+} state in the crystal phase of nanoceria and the interconversion energy is very low between these two oxidation states⁵⁹ which enables the formation of oxygen vacancies inside the crystal. This unique redox property makes nanoceria suitable for various applications like catalyst in automobile exhaust, an agent with antioxidant applications, solid oxide fuel cells (SOFC), as a sensor for detecting oxygen gas, in membrane systems for oxygen permeability, used as a catalyst for chemical reactions which involves oxidation.⁶⁰⁻⁶³ The ratio of Ce^{3+} to Ce^{4+} present in the crystal of nanoceria plays the most important role in exhibiting its redox properties. According to literature, the size and surface morphology of the nanostructures of ceria is responsible for the Ce^{3+} amount present in the facets of crystal.^{58, 64} If the overall dimension of the nanoceria crystal reduces there are more favorable chances of high Ce^{3+} to Ce^{4+} ratio due to high surface to volume ratio.⁶⁵ When the oxidation state of nanoceria reduces from Ce^{4+} to Ce^{3+} , it is speculated that there is generation of superoxide anions, thus contributing for the generation of harmful hydroxyl radical and acts as a prooxidant. Another postulation concludes that Ce^{3+} can react with the hydroxyl radicals and contributes for the antioxidant properties.^{10, 17, 22, 25} Thus, we can state that the valance state of cerium can play a vital role in deciding whether CeO-NPs will exert a protective property or a toxic role when exposed to a biological system.⁶⁶ The dual valance state has also been utilized to design ceria nanocluster based ROS sensor.⁶⁷ We can conclude from the previous research that the valance state of CeO-NPs can decide whether they are prooxidant or antioxidant and when the ratio of $\text{Ce}^{3+}/\text{Ce}^{4+}$ increases the toxicity gets enhanced thereby decreasing its antioxidant potential. This shows the dual role of nanoceria as an antioxidant as well as prooxidant depending on size, surface morphology and the ratio of $\text{Ce}^{3+}/\text{Ce}^{4+}$ on the surface of the crystal.

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Conflict of Interest

The authors declare no conflict of interest.

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