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Cerium Oxide Nanoparticles as Antioxidants

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Toxic stresses brought on by conditions including infection, allergies or smoking cause a surplus of reactive oxygen species (ROS) to be produced in the body (Liu & Schubert, 2009; Schubert et al., 2006). These highly reactive free radicals, such as superoxide or the hydroxide radical, cause serious damage, known as oxidative stress, to cells by removing electrons from cellular lipids and proteins (Rzigalinski et al., 2006). Cells have the means to defend themselves from ROS, but with age and disease this defense mechanism falters (Singh, Cohen, & Rzigalinski, 2007). A cell's natural defense against ROSs is through the use of antioxidants, and other mechanisms such as regulatory enzymes, but when ROS production is too much for a cell, medicinal antioxidants can be introduced (Andreescu, Leiter, & Erlichman, 2010). The antioxidants brought in are very limited in their ability to remove ROS: a single antioxidant molecule can remove only one free radical and the antioxidants are targeted only to a specific location on the cell – not necessarily the right location (Singh et al.). While ROSs are damaging in the cell, it is important to note that ROSs do have a purpose in the body related to the immune system (Nathan & Shiloh, 2000). However, a surplus of them requires counteraction to maintain the body's balance.

Cerium oxide as a free radical scavenger

Schubert, Dargusch, Raitano, and Chan (2006) found that cerium oxide nanoparticles have beneficial effects when it comes to reducing ROS quantities in a biological system and that cerium oxide's chemical properties make it resemble a free radical scavenger or an antioxidant. Cerium is an element found in the lanthanide series on the periodic table. It can exist in the 3+ or 4+ valence states and can switch between the two states in order to reduce or oxidize other compounds. Cerium oxide (CeO_2), also known as ceria, has special reducing properties due to its lattice structure and its high likelihood of developing oxygen vacancies, a type of defect in the structure. The oxygen vacancies, as well as the very mobile lattice oxygen on the ceria's surface means electrons are shuffling around and cerium is able to convert between its two valence states easily. When cerium oxide is in a reduction-oxidation environment, the movement of oxygen in and out of the compound a redox reaction will occur (Andreescu et al., 2010; Schubert et al., 2006).

In redox reactions, cerium oxide is capable of reducing the harmful free radicals (Rzigalinski et al., 2006; Singh et al., 2007). In addition, as long as there is still oxygen fueling the reaction, cerium oxide is able to regenerate and continue scavenging, unlike traditional antioxidants (Andreescu et al., 2010). At the nanoscale, cerium oxide has even greater antioxidant properties mainly due to the increase in surface area which increases the cerium oxide reactivity, resulting in a higher frequency of oxygen vacancy interactions (Singh et al.). Nanoparticles are also more likely to enter the cell because they are so small (Rzigalinski et al.). All of these traits make cerium oxide nanoparticles seem to be more effective antioxidants than traditional antioxidants.

Applications

The antioxidant properties of nanoceria have as many applications as there are negative effects caused by ROS. There have been studies suggesting that nanoceria can fight vision loss (Suh, Suslick, Stucky, & Suh, 2009), neurodegenerative disorders, and even aging (Liu & Schubert, 2009; Singh et al., 2007). The majority of research on cerium oxide nanoparticles has been associated with the nervous system since the brain suffers the most from oxidative stress (Singh et al.). Research done by Schubert et al. (2006) dealt with the HT22 cell line found in the rodent nervous system. To cause programmed cell death, HT22 mitochondria create an excess amount of ROS in order to break down the cell. In the experiment, glutamate was used to create stress on the HT22 cells in order to initiate the cell death program and stimulate the production of ROS. Using aluminum oxide nanoparticles as a control, the study determined that nanoceria do in fact act as antioxidants and can increase the longevity of HT22 cells under oxidative stress. The protection of nervous system cells suggests that cerium oxide nanoparticles are neuroprotective agents.

An area of central concern is the brain, which is constantly under high pressure from oxidative stress. The damage caused can lead to neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's as well as more damage brought about by trauma (Singh et al., 2007). Nanoceria may have the ability to significantly reduce the likelihood of developing neurodegenerative diseases, if

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properly implemented on cells in the central nervous system. Singh et al. tested the protective qualities of nanoceria on neurons from trauma-induced damage. The investigation showed a 75% reduction of damage from the trauma when compared to the control. This data demonstrates that nanoceria effectively reduces the likelihood of trauma, and may potentially offer similar effects for other diseases related to the central nervous system, caused by oxidative stress.

Singh et al. (2007) also tested the effects of nanoceria on the lifespan of fruit flies. The fruit flies ingested 10 nM nanoceria, incorporated in their daily diet, throughout their lifetime. The study found that there was an increase of 18% in the maximum lifespan of the specimens. However, concentrations below 1 nM and above 1 μM had less effect on the lifespan, suggesting that there is level of reduction that balances the damage and benefits ROSs cause to cell. This anti-aging effect shows best how effective nanoceria can be. If the nanoparticles are engineered for pharmacological purposes, the applications will be numerous.

Discussion

Toxicity is a major concern that needs to be addressed when it comes to introducing cerium oxide into the body. One study found that cerium oxide does have toxic effects; nanoceria is capable of raising the level of ROS and causing damage to cell membranes (Lin, Huang, Zhou, & Ma, 2006). The study did not, however, explore whether or not the toxicity of cerium oxide was size-dependent. Schubert et al. (2006) did consider the possibility of size-dependent toxicity and found that with cerium oxide nanoparticles smaller than 1 μm there was very little toxic effect on the HT22 cells tested. Concentra-tions of the 1 μm nanoparticles greater than 20 μg/mL did show signs of toxicity, however. Schubert et al.'s study demonstrates that toxicity of nanoceria does in fact depend on the size of the particle and its concentration in the system, meaning that if properly prepared, cerium oxide could be safe in the body.

Although ROSs are very harmful to cells, they are vital in a biological system. Without free radicals, a cell's susceptibility to pathogens increases. The reason for which ROS can be considered both protective and damaging to cells is the nonspecificity of its target. ROS could attack a pathogen and protect the host cell, or it could end up attacking the host cell itself (Nathan & Shiloh, 2000). By introducing nanoceria into the body, the beneficial and damaging effects of ROS are erased. Other than the possibility of preventing some pathogenic immunity, cerium oxide nanoparticles have no foreseeable downsides, as they are non-toxic when prepared in the proper concentration and particle size (Schubert et al., 2006).

Conclusion

Cerium oxide nanoparticles hold great potential in the field of medicine. Their chemical and physical properties allow them to act as advanced antioxidants that are able to regenerate and reduce the amount of ROS very effectively to minimize oxidative stress on cells. The reduction of oxidative stress may prevent several conditions that arise in conjunction with ROSs, such as trauma or Alzheimer's. However, the removal of ROS from the body might reduce immunity to certain pathogens, so that a balancing agent becomes necessary. Because cerium oxide does show some signs of toxicity, precautions are needed for the preparations—specifically the concentration and size of particle—for the nanoparticles if they are to be used in the body. The limited research on the use of nanoceria as antioxidants is recent, and so far has few contributors to the topic. Further research on nanoceria could lead to sit-specific targeting and even stronger antioxidant properties.

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