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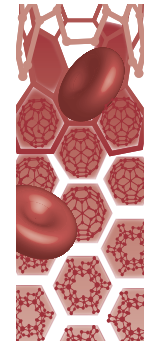

Cerium oxide nanoparticles: a 'radical' approach to neurodegenerative disease treatment

Despite advances in understanding the factors that cause many neurodegenerative diseases (NDs), no current therapies have yielded significant results. Cerium oxide nanoparticles (CeONPs) have recently emerged as therapeutics for the treatment of NDs due to their antioxidant properties . This report summarizes the recent findings regarding CeONPs in treatment of various NDs, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, ischemic stroke and amyotrophic lateral sclerosis. Interest in CeONPs as a potential nanomedicine for NDs has increased due to: their ability to alter signaling pathways, small diameter allowing passage through the blood–brain barrier and scavenging of reactive oxygen species. Due to these properties, CeONPs could eventually revolutionize existing treatments for NDs.

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Neurodegenerative diseases (NDs) (Figure 1) are the fourth largest and most debilitating disorders of the CNS which ultimately result in death. Globally, about 10 million people suffer every year from NDs. Within a decade, this number is expected to rise by 20% due to the increase in the aging population [1–3]. Among all NDs, Alzheimer's diseases (ADs) and Parkinson's diseases (PDs) are the most prevalent and intensely studied [4] (Figure 2).

According to the Alzheimer's Association's estimates for 2016, over 5.3 million Americans are living with AD [2,4]. By 2050, if new treatments are not discovered, numbers could increase to 11–16 million, with one new case appearing every 33 s [4,6]. The projected cost of providing care for Alzheimer's patients in 2016 is $236 billion and if the trend continues, this cost is estimated to rise to $1.1 trillion annually by 2050 [4]. The most commonly observed symptoms of Alzheimer's patients are memory loss, spatial disorientation, aggression and cerebral atrophy [1,4,7]. Although the exact cause of the disease is not well understood, research conducted to date indicates that Alzheimer's results from a combination of genetic and environmental factors [4,8–9]. According to many studies, the accumulation of toxic proteins, specifically tau tangles and β-amyloid plaques, and their movement in and out of brain neurons serve as the major cause for Alzheimer's [7,10].

After AD, PD is the second most prevalent ND [11]. The US National Institute for Neurological Disorders and Stroke have estimated that around one million people live with PD and every year about 50,000 more are diagnosed. Globally, more than 10 million people are living with PD. According to a 2016 report from the American Parkinson Disease Association, the cost of care for Parkinson's patients in the USA is $25 billion, and could more than double by 2040 [12]. The main cause of Parkinson's is the aggregation of the α-synuclein (SNCA) gene [10]. Symptoms of Parkinson's include bradykine-

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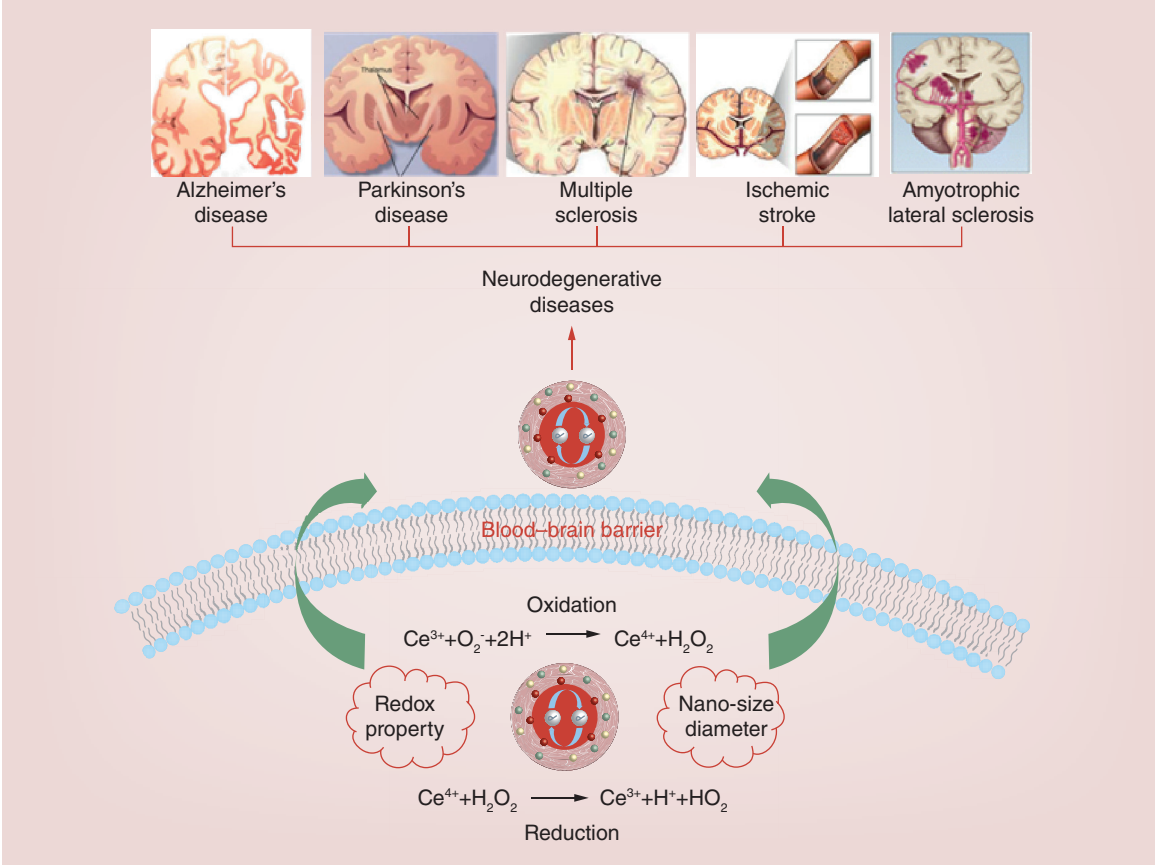

Figure 1. Schematic representation of cerium oxide nanoparticles as a vehicle for therapeutics and their innate antioxidant properties for the effective treatment of neurodegenerative diseases. The low reduction potential and the co-existence of mixed valence states play an important role in scavenging reactive oxygen species, the prime suspect in CNS damage across all the diseases mentioned in this report. Additionally, cerium oxide nanoparticles can cross the blood–brain barrier due to their nanoscale diameters [5].

sia, muscle rigidity, depression, resting tremors, skin problems, constipation and sleep disruptions [7,10,13]. Following AD and PD, the other debilitating NDs are multiple sclerosis (MS), ischemic stroke (IS) and amyotrophic lateral sclerosis (ALS), although these are relatively uncommon in the USA [1,14].

The current existing treatments for Alzheimer's only alleviate symptoms but do not hinder the progression of the disease. Additionally, of all the theories that have been proposed for treating Alzheimer's, only β-amyloid (Aβ) cascade and tau hyperphosphorylation have been widely accepted [7,13]. The drugs approved so far by the US FDA for Alzheimer's treatment are classified as cholinesterase inhibitors, which increase concentrations of acetylcholine and subsequent neurotransmitter activity [7,15]. These include tacrine (1993), donepezil (1996), rivastigmine (2000), galantamine (2001), memantine (2003) and a dual-drug combination of donepezil and memantine (2014) [7,15]. Other than these medications, clinical methods used for Alzheimer's treatment are brain imaging and neuropsychological testing, which are known to be 85% accurate [16].

The existing treatments for PD include surgical methods (thalamotomy, pallidotomy or insertion of deep brain stimulation devices) and a drug regimen of levodopa and carbidopa, which delays the conversion of levodopa to dopamine until it reaches the brain [1,17–19]. Various stem cell models (mesenchymal, neural and embryonic) have also been proposed by different researchers for potential treatment of PD [20–22]. On the other hand, current treatments for MS include immunomodulatory and immunosuppressive agents [14], whereas aspirin, anticoagulants, antihypertensive drugs, antiplatelet medications and surgical methods are available for IS [23,24].

Currently, treatments for NDs are limited due to not only the relative ineffectiveness of therapeutics, but also the many protective barriers surrounding CNS. One of these protective coverings of the brain is the blood–brain barrier (BBB), which restricts the passage of exogenous substances to the brain [1,4,25]. Due to this, new therapeutics with the ability to cross the BBB unrestricted is urgently needed for effective treatment of NDs [26]. To this end, nanotechnology repre-

sents an innovative and promising approach due to the unique properties of nanoparticles, which allow them to cross the BBB for therapeutic effect [25]. They also exhibit targeted delivery with sustained drug release for improved quality of health for those afflicted by NDs [25].

Many studies have reported that oxidative stress plays a pivotal role in the development of all NDs. Oxidative stress results from the production of reactive oxygen species (ROS), which are produced in both the mitochondria (by monoamine oxidase and complexes I and III) and the cytosol (by NADPH and xanthine oxidases) as byproducts of healthy cellular activity [11]. Excessive production of ROS seen in NDs (namely hydrogen peroxide, super oxide radicals, hydroxyl radicals and peroxynitrite), however, can damage cells, requiring exogenous aid in the reduction of these compounds [11,27–32]. With this in mind, antioxidants are commonly employed to alleviate oxidative stress and, subsequently, the symptoms associated with these diseases [27,33–35]. However, antioxidants by themselves cannot cross the BBB, further necessitating the importance of nanoparticle-based antioxidant delivery systems. One such delivery system is cerium oxide nanoparticles (CeONPs), which continuously scavenge ROS [11,27–31]. This is accomplished by the transi-

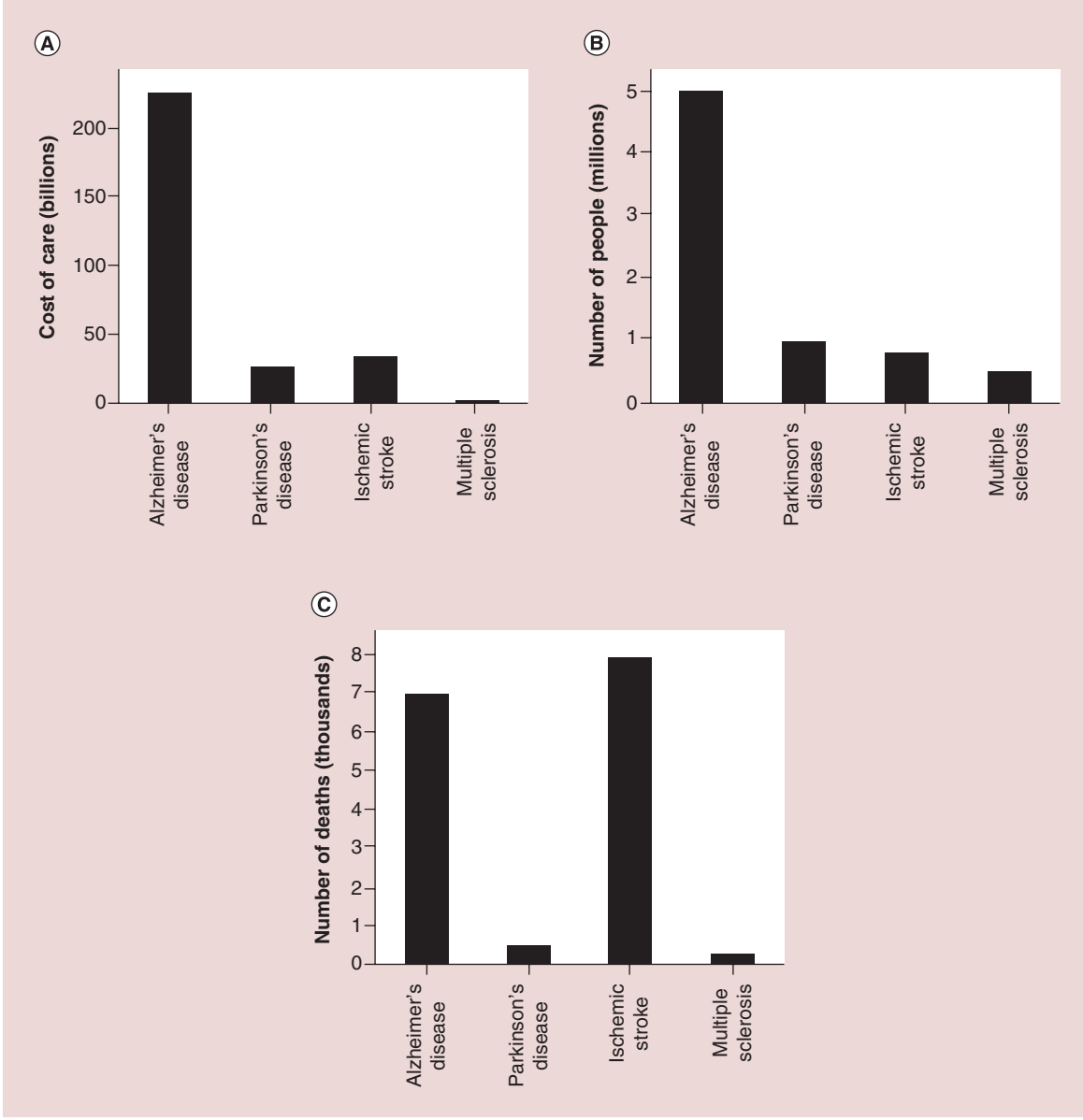

Figure 2. Statistical representation of the impact of NDs. **(A)** Current global economic burden of neurodegenerative diseases, **(B)** current number of individuals living with neurodegenerative diseases in the USA and **(C)** average annual deaths due to neurodegenerative diseases.

tion between cerium's +3 and +4 oxidation states at the particle's surface, which allows CeONPs to regenerate as ROS concentrations increase or decrease [25,29,36–43]. This type of redox activity is akin to that of superoxide dismutase (SOD) and catalase, two endogenous enzymes that reduce ROS [39,40].

Though transport to BBB has been confirmed, there have also been instances where CeONPs persist (up to 90 days) and subsequently biotransform in the liver, spleen, kidneys and lungs before passing the BBB, convey some degrees of toxicity [32,44–47]. However, this is typically only observed in cases where CeONPs exceed 5 nm in diameter [25,32,44–47]. Cases where CeONP size is more carefully monitored and controlled (less than 3 nm) show increased uptake into the BBB, as well as reduced concentration in the aforementioned organs over time (Figure 3) [25].

Due to their antioxidant potential, CeONPs have been found to be effective against pathologies associated with chronic oxidative stress and inflammation [5,36,48–50]. Such properties, however, have shown some inconsistencies when this compound is converted to therapeutic CeONPs. The efficacy of the resulting CeONPs' physicochemical properties strongly depends upon many factors of the initial synthesis (catalyst, etc.), which can have detrimental effects on the particle's surface chemistry [51]. With this in mind, this review will address the attractive therapeutic approaches of CeONPs in the treatment of NDs, with particular emphasis on AD and PD, as these diseases are the most studied with regard to CeONP treatment. The therapeutic application of nanomaterials has been a focus of numerous studies in the past decade. Due to its unique redox properties, cerium oxide (ceria) is finding widespread use in the treatment of medical disorders caused by the reactive oxygen intermediates. The radical-scavenging role of ceria nanoparticles (nanoceria) have been established, as well as the autocatalytic ability of nanoceria to regenerate under various environmental conditions. The synthesis of nanoceria in biocompatible media has also been reported along with cell viability in order to determine the potential use of nanoceria in biomedical applications.

Role of CeONPs in Alzheimer's treatment

Immense research has been carried out to determine effective therapies utilizing the potent antioxidant activity of CeONPs for the treatment of AD. The brain-derived neurotrophic factor (BDNF) protein, which plays a key role in memory formation and storage, are found at reduced levels of concentration in individuals afflicted by Alzheimer's. Reduced BDNF levels are linked to the degeneration of specific neurons, eventually leading to dementia. Toward this end, D'Angelo *et al.* conducted experiments on SH-SY5Y human neuroblastoma cells, treated with Aβ cell line [48]. The cells were forced to undergo neuronal differentiation by rapidly forming fibrillary aggregates, which are highly cytotoxic to neuronal cells. Results showed that when these cells were treated with CeONPs, the BDNF signal transduction pathways were altered, which protect the neuronal cells against apoptosis induced by Alzheimer's injury. In another report, Dowding and colleagues reported that nitrosative stress and mitochondrial dysfunction are responsible for the pathogenesis of Alzheimer's. They concluded that the treatment with CeONPs reduce the level of ROS, endogenous peroxynitrate, Aβ-induced mitochondrial fragmentation, DRP1S616 hyperphosphorylation and neuronal cell death [52].

Additionally, metal ions play a key role in Aβ-aggregate deposition resulting in neurotoxicity and the formation of ROS. Metal dysregulation and oxidative stress are considered to be pathological targets for AD. Qu and coworkers presented the synergistic effect between the integrated anti-aggregation property of metal chelators and antioxidant property of CeONPs for potential Alzheimer's treatment [53]. They reported that CeONPs can effectively inhibit aggregation of Aβ, decrease cellular ROS and protect cells from Aβ-related toxicity due to their unique selectivity for toxic metal ions and antioxidant properties.

In another report, Singh *et al.* established that the size, composition and surface area of CeONPs play an important role in their antioxidant activity [54]. Ultraviolet radiation (UV), hydrogen peroxide (H_2O_2) and toxic fragments of Aβ and $Aβ_{1–42}$ peptides produce free radicals, which are known to be a key factor in Alzheimer's pathology. The antioxidant activity and neuroprotective capacity of three different types of functional CeONPs (7 nm, 10 nm and Fe-doped) were synthesized and analyzed by electron paramagnetic resonance. The results showed that 10 nm CeONPs more effectively reduced UV- and H_2O_2-induced neuronal cell death when compared with the 7 nm CeONPs. In fact, the 10 nm CeONPs not only protected neurons from various free radical associated damage and $Aβ_{1–42}$ induced toxicity, but also extended the life span of brain neurons. The synthesized Fe-doped CeONPs were found to nullify the antioxidant protection.

Cimini *et al.* developed PEG-coated CeONPs conjugated with anti-amyloid β-antibodies and examined its effect on neuronal survival and the BDNF pathway [55]. Aβ-PEG-CeONPs were specifically targeted to Aβ aggregates by modulating the BDNF signaling pathway, thus making anti-Aβ CeONPs a potential

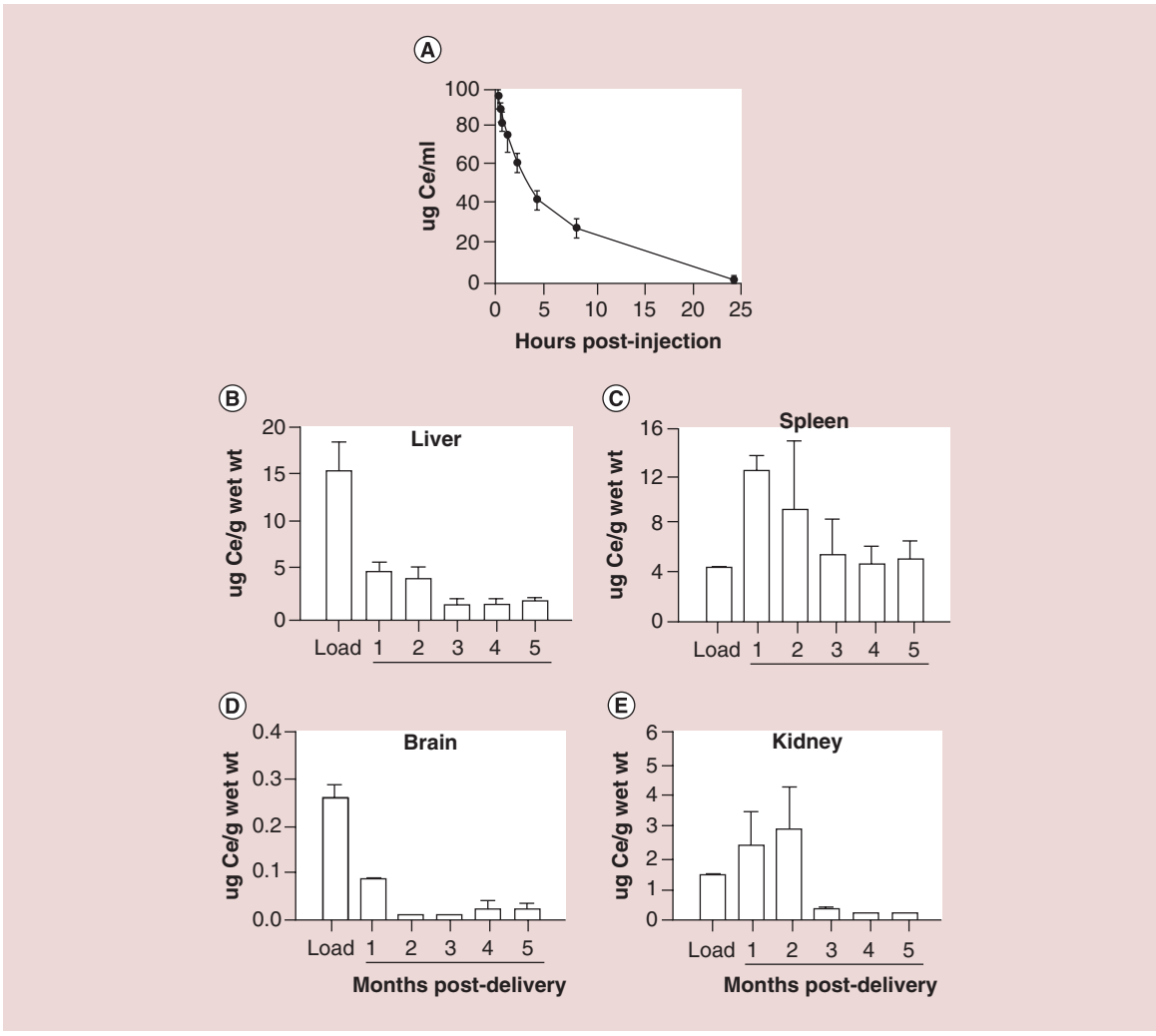

Figure 3. Cerium oxide nanoparticles' half-life and tissue clearance. (A) A total of 10 mg/kg of cerium oxide nanoparticles was administered intravenously to healthy Sprague–Dawley rats, and blood was collected over a 24 h period. Ceria content was measured by Inductively coupled plasma–mass spectrometry. **(B–E)** Healthy SJL/J mice were injected with one intravenous 20 mg/kg cerium oxide nanoparticles dose, and various tissues were harvested 24 h (Load) or 1, 2, 3, 4 or 5 months post administration. Liver **(B)**, spleen **(C)**, brain **(D)** and kidney **(E)** tissues were analyzed by Inductively coupled plasma–mass spectrometry for ceria content expressed as micrograms of Ce per gram of tissue wet weight (μg Ce/g wet wt).
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candidate for therapy of NDs. In a recent review, Nelson *et al.* have highlighted the importance of physiochemical properties and reaction mechanisms of CeONPs for their unique antioxidant and ROS scavenging properties [56]. Oxidative stress in mitochondria is an important attribute for the pathogenesis of AD. Kwon *et al.* have described a new synthetic strategy using triphenylphosphonium-conjugated CeONPs to reduce morphological mitochondrial damage [57]. In their studies, selective targeting of CeONPs to mitochondria led to suppression of neuronal death in mice with 5XFAD transgenic AD. Their results suggested that CeONPs can be a potential therapeutic candidate for mitochondrial oxidative stress.

Role of CeONPs in Parkinson's treatment

So far, few reports have been made available for treatment of PD with CeONPs. The ongoing research efforts utilizing the antioxidant properties of CeONPs could bring forth potential therapeutic options for PD in the near future. Many studies suggest that a number of environmental factors are associated with the etiology of PD [58,59]. One such factor is exposure to heavy metals. In the past few years, manganese exposure has been linked to occupational forms of Parkinson's-like diseases. Pinna *et al.* studied the antioxidant effect of size-controlled CeONPs in manganese exposed-catecholaminergic cells (PC12) [58]. This was done by analyzing their concentration during cell metabolism

via MTT and trypan blue assays. This group also analyzed CeONPs' internalization by Raman and confocal microscopy [58]. To further develop an effective combined treatment, they tested CeONPs alone and in association with L-DOPA, the latter showing significantly reduced manganese chloride-induced oxidative stress. They evaluated the protective role of CeONPs on the metabolism of catecholamines by monitoring the intracellular concentration of dopamine and its metabolites using liquid chromatography. Results showed the protective role of CeONPs on both PC12 cells and dopamine metabolism, making it an effective alternative for the treatment of Parkinson's-like diseases induced by chronic manganese exposure.

Dillon *et al.* demonstrated for the first time that CeONPs could preserve striatal dopamine and protect dopaminergic neurons in the substantia nigra in MPTP-mouse model of PD [59]. Additionally, they described that the dosage of CeONPs at which neuroprotection was observed to be very low (0.5–5 µl). Results showed that in the substantia nigra, CeONPs significantly increased the levels of tyrosine hydroxylase and displayed similar neuron counts akin to those of animals not exposed to MPTP.

Role of CeONPs in the treatment of other neurodegenerative disorders

Multiple sclerosis

The efficacy of CeONPs in neutralizing biologically generated free radicals *in vitro* has been explored extensively [25]. In general, CeONPs can be stabilized with citrate or polyethylene glycol, though they have highly negative ζ potentials and accumulate in the liver and spleen [25,32,44–47]. To counteract this, Heckman *et al.* synthesized unique CeONPs having smaller diameter (2.9 nm) and less negative ζ potential [25]. They stabilized these CeONPs with a stable citrate-EDTA coating, which resists being washed away in physiological solutions. The biological effects of these custom-synthesized CeONPs was observed in a murine mouse model with MS induced by free radical mediated oxidative injury. Interestingly, when this formulation is injected intravenously, it reaches the brain and scavenges the ROS, alleviating the clinical symptoms and motor deficits in the mice. They found that CeONP-treated animals exhibit reduced ROS in the brain, demonstrating that CeONPs retain their antioxidant properties and can potentially be used for the treatment of oxidative stress in MS.

Ischemic stroke

Estevez *et al.* explored the use of CeONPs as a potential therapeutic agent for IS in a mouse hippocampal brain slice model of cerebral ischemia [60]. They evaluated CeONPs' neuroprotective activity in peroxynitrate-induced ischemic mouse brain and found that it remarkably decreased the level of 3-nitrotyrosine, a modified tyrosine protein residue by the peroxynitrate radical. Based on their experiment, they reported that CeONPs reduced the ischemic cell death by approximately 50%. In another study, Kim *et al.* have shown that pegylated-CeONPs with uniform diameter (about 3 nm) can effectively scavenge ROS and reduce the neuronal cell death in IS [61]. Furthermore, reduced infarct volumes were observed *in vivo* with optimum dosage of CeONPs.

Amyotrophic lateral sclerosis

DeCoteau *et al.* have found promising results from the citrate-EDTA stabilized CeONPs with the ability to neutralize both ROS and nitrogen species in the $SOD1^{G93A}$ mouse model of ALS [62]. The mice were treated twice weekly at the onset of muscle weakness. CeONPs treatment preserved muscle function and extended lifespans to approximately 33 days. They concluded that these CeONPs displayed catalase activity in addition to their reputation as an antioxidant.

Conclusion & future perspective

For the past few years, the role of CeONPs for the treatment of cancer, neurodegenerative and ocular diseases have been investigated in great detail. Oxidative stress still continues to be one of the major factors responsible for the etiology of NDs. The presence of mixed valence states and extraordinary antioxidant properties possessed by CeONPs make them ideal for the treatment of these diseases. The unique redox property of cerium oxide makes it a potent antioxidant when compared with other ROS modulators, which are hampered by their short half-lives and the ability to scavenge ROS by 1:1 proportion. In addition, existing treatments for NDs, including delivery of therapeutic agents directly to the brain, still remains a major challenge due to the protective barriers, BBB, in the CNS. Due to its small size and unique redox properties, several reports have recently demonstrated the promising applications of CeONPs for Alzheimer's, Parkinson's and other NDs.

With regard to Alzheimer's and Parkinson's, there should be further investigation to establish other properties of CeONPs. Particularly, the ROS-scavenging ability of CeONPs seem to overshadow its' other potential properties. In the future research may be performed with respect to the drug-encapsulating potential of CeONPs and its synergistic therapeutic effect on oxidative stress reduction. Future research should also focus on the effects of CeONPs on the aggregation, fibrillation and kinetics of CNS proteins, particularly the α-synuclein, Aβ-amyloid and tau protein families.

In conclusion, it is evident that CeONPs are extremely useful for the treatment of AD, though fewer reports available for PD, MS, IS and ALS have displayed some degree of success as well. The key to CeONPs' success lies in increasing the amount transported through the BBB, as well as controlling the unsolicited accumulation in various organs. Therefore, many more *in vitro* and *in vivo* experiments exhibiting these diseases should be performed to evaluate the potential efficacy of CeONPs before moving on to human clinical trials.

Financial & competing interests disclosure

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Executive summary

- Cerium oxide nanoparticles (CeONPs) are well known for their potential therapeutic applications in the treatment of neurodegenerative diseases, due in large part to their remarkable property to reduce oxidative stress in the damaged cells of the CNS. This strong antioxidant property results from cerium oxide's innate ability to switch between Ce^{+3} and Ce^{+4} oxidation states.
- In Alzheimer's disease, CeONPs are able to alter the brain-derived neurotrophic factor signal transduction pathway, retarding the apoptotic effect of the disease in neuronal cells. They also exhibited the ability to decrease Aβ-aggregation when conjugated with metal chelators or PEG coatings.
- In Parkinson's disease, CeONPs displayed successful reduction of neuronal cell damage induced by manganese exposure. Additionally, they also appeared to preserve the metabolism of catecholamine and dopamine, which are typically crippled when exposed to heavy metals.
- CeONPs displayed promising results in the treatment of other neurodegenerative diseases, although more extensive research needs to be conducted in these areas. Currently, it is known that CeONPs are effective at restoring limb motor function in multiple sclerosis and amyotrophic lateral sclerosis mice models, and scavenging peroxynitrate reactive oxygen species in ischemic stroke models.

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