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Antibody-conjugated PEGylated cerium oxide nanoparticles for specific targeting of Aβ aggregates modulate neuronal survival pathways

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ABSTRACT

Oxidative stress has been found to be associated with the progression of neurodegenerative diseases such as Alzheimer's, Parkinson's, Lou Gehrig's, etc. In the recent years, cerium oxide nanoparticles (CNPs) have been studied as potent antioxidant agents able to exert neuroprotective effects. This work reports polyethylene glycol (PEG)-coated and antibody-conjugated CNPs for the selective delivering to Aβ aggregates, and the protective effect against oxidative stress/Aβ-mediated neurodegeneration. In this study PEG-coated and anti-Aβ antibody-conjugated antioxidant nanoparticles (Aβ-CNPs-PEG) were developed, and their effects on neuronal survival and brain-derived neurotrophic factor (BDNF) signaling pathway were examined. Aβ-CNPs-PEG specifically targets the Aβ aggregates, and concomitant rescue of neuronal survival better than Aβ-CNPs, by modulating the BDNF signaling pathway. This proof of concept work may allow in the future, once validated in vivo, for the selective delivery of CNPs only to affected brain areas.
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1. Introduction

Amyloid-beta 1–42 (Aβ), local inflammation and the consequent production of reactive oxygen species are considered the major etiological and pathological factors in the promotion of neurodegenerative diseases such as Alzheimer's disease (AD) [1–6]. To date, the use of multiple doses of antioxidants to counteract these pathological conditions has met with only limited success [7]. Recently, we have discovered that cerium oxide nanoparticles (CNPs) are redox active and biocompatible materials with both superoxide dismutase [8] and catalase mimetic activity [9]. Among the lanthanide series of elements, cerium is distinctive in that it has two partially filled subshells of electrons, 4*f* and 5*d*, with many excited substates, resulting in a valence structure that undergoes significant alterations depending on the chemical environment [10–13]. Predominate +3 oxidation states on the surface of CNPs are responsible for their unique antioxidant properties [14,15]. We have shown that a single dose of CNPs prevents retinal degeneration induced by peroxides [16]. In an in vitro model, one low dose exerted radical scavenging activity and neuroprotective effects for a long duration and under multiple insults, suggesting the possibility of regenerative activity. Therefore, CNPs have been suggested as a nanopharmacological approach to diseases associated with oxidative stress [17–22]. Previously, using an AD human in vitro model, we have confirmed the antioxidant properties of bare CNPs. We have also demonstrated that CNPs do not act as mere antioxidant agents, but seem to regulate signal transduction pathways involved in neuroprotection [23]. The novelty of the approach described in this work takes advantage of nano- and biotechnological approaches to enhance the specific target of CNPs. We synthesized PEG-coated CNPs and subsequently conjugated anti-amyloid β antibody to the PEG-coated CNPs, obtaining selective delivery to the Aβ plaques and a concomitant increase in neuronal survival. Our results demonstrate that CNPs-Ab may be a potential candidate for anti-neurodegenerative therapy.

2. Materials and methods

2.1. Materials

Triton X-100, dimethylsulfoxide (DMSO), sodium dodecylsulfate (SDS), Tween20, bovine serum albumine (BSA), L-glutamine,

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