Sustained protection against photoreceptor degeneration in tubby mice by intravitreal injection of nanoceria

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We previously reported that nanoceria can slow retinal degeneration in the tubby mouse for two weeks by multiple systemic injections. However, the long-term protection of retinal structure and function by directly deliver of nanoceria to the eye had not been explored. In this study, 172 ng of nanoceria in 1 μl saline (1 mM) were intravitreally injected into tubby P7 pups and assays were performed at P28, P49, P80 and P120. The expression of antioxidant associated genes and photoreceptor-specific genes was significantly up regulated, the mislocalization of rod and cone opsins was decreased, and retinal structure and function were protected. These findings demonstrate that nanoceria can function as catalytic antioxidants in vivo and may be broad spectrum therapeutic agents for multiple types of ocular diseases.

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1. Introduction

The tubby mouse was naturally generated by a splicing mutation in the Tub gene [12,15]. It exhibits early and rapid retinal and cochlear degeneration, maturity onset of obesity, resistance to insulin and gradual reduction of fertility. These characteristics are similar to those of human Usher's syndrome [3,4]. Our previous study revealed that the photoreceptor degeneration occurs at P14 [5] and cell death peaks at P19 [6]. Almost half of the photoreceptors are dead by P28 and retinal function is undetectable around 2 months of age [5]. As a member of the TUB family, the TUB protein has been suggested to function as a transcription factor and to be involved in protein trafficking [7]. Mutation of the TUB protein results in mislocation of photoreceptor-specific proteins, rhodopsin, arrestin and transducin [5]. Although the mechanism underlying the defect in the Tub gene and photoreceptor cell death is not known, published data suggest that inherited ocular diseases proceed through oxidative stress [8–10]. Excessive amounts of reactive oxygen species (ROS) cause photoreceptor cell damage and subsequent cell apoptosis [11]. At present, there are no effective therapies to treat and cure inherited ocular diseases. Classical antioxidant treatments can slow the retinal degeneration but the pharmaceutical longevity is an issue because daily supplementations are needed.

Nanoceria (cerium oxide nanoparticles) have large surface area to volume ratios and form oxygen vacancies which enable them to catalytically and regeneratively scavenge free radicals and destroy the ROS [12–14]. Nanoceria have been shown to decrease the amount of ROS thereby protecting adult rat spinal cord neurons in vitro [15], and down regulate the expression of a biomarker for myofibroblastic cells and prevent the invasion of tumor cells [16]. Our lab previously reported that nanoceria can protect photoreceptor cells from oxidative stress-induced damage in a light damaged albino wild type rat model [17]. In very low density lipoprotein receptor knockout (Vldrl−/−) mice, nanoceria decreased oxidative stress, down regulated vascular endothelial growth factor (VEGF) and caused the regression of existing intraretinal and subretinal neovascularizations [18]. In tubby mice, by regulating cell survival/apoptosis signal transduction pathways, nanoceria delayed photoreceptor degeneration and protected retinal function for up to 2