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Microspheres as intraocular therapeutic tools in chronic diseases of the optic nerve and retina

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ABSTRACT

Pathologies affecting the optic nerve and the retina are one of the major causes of blindness. These diseases include age-related macular degeneration (AMD), diabetic retinopathy (DR) and glaucoma, among others. Also, there are genetic disorders that affect the retina causing visual impairment. The prevalence of neurodegenerative diseases of the posterior segment is increased as most of them are related with the elderly. Even with the access to different treatments, there are some challenges in managing patients suffering retinal diseases. One of them is the need for frequent interventions. Also, an unpredictable response to therapy has suggested that different pathways may be playing a role in the development of these diseases. The management of these pathologies requires the development of controlled drug delivery systems able to slow the progression of the disease without the need of frequent invasive interventions, typically related with endophthalmitis, retinal detachment, ocular hypertension, cataract, inflammation, and floaters, among other. Biodegradable microspheres are able to encapsulate low molecular weight substances and large molecules such as biotechnological products. Over the last years, a large variety of active substances has been encapsulated in microspheres with the intention of providing neuroprotection of the optic nerve and the retina.

The purpose of the present review is to describe the use of microspheres in chronic neurodegenerative diseases affecting the retina and the optic nerve. The advantage of microencapsulation of low molecular weight drugs as well as therapeutic peptides and proteins to be used as neuroprotective strategy is discussed. Also, a new use of the microspheres in the development of animal models of neurodegeneration of the posterior segment is described.

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Abbreviations: AMD, age-related macular degeneration; ARPE, arising retinal pigment epithelial cells; b-FGF, basic fibroblast growth factor; BSA, bovine serum albumin; BDNF, brain-derived neurotrophic factor; CNS, Central Nervous System; CNTF, ciliary neurotrophic factor; CD, circular dichroism; CNV, corneal neovascularization; COX, cyclooxygenase; DR, diabetic retinopathy; DENAQ, diethylamine-azobenzene-quaternary ammonium; ERG, electroretinography; ELISA, Enzyme-Linked ImmunoSorbent Assay; EPO, erythropoietin; GDNF, Glial cell-line derived neurotrophic factor; GFLs, GDNF family ligands; HUVECs, Human Umbilical Vein Endothelial *Cells*; INL, inner nuclear layer; IPL, inner plexiform layer; IDDS, intraocular drug delivery system; IOP, intraocular pressure; MMP-2, matrix metalloproteinase 2; MS, microspheres; NSAIDs, nonsteroidal anti-inflammatory drugs; ONL, outer nuclear layer; PBS, phosphate-buffered saline; PLGA, poly(lactic-*co*-glycolic) acid; PEAs, poly(ester amide)s; PLA, poly(lactic) acid; PBAE, poly-beta amino ester; PEG, polyethylene glycol; QAQ, quaternary ammonium-azobenzene-quaternary ammonium; RPCs, radial peripapillary capillaries; RGCs, retinal ganglion cells; RPE, retinal pigment epithelial cells; RP, retinitis pigmentosa; PDE, rod-phosphodiesterase; PDE, rod-phosphodiesterase; SEC, size-exclusion chromatography; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; TGF-β, transforming growth factor-β; TA, triamcinolone acetonide; FDA, US Food and Drug Administration; VEGF, vascular endothelial growth factor; Vit E, vitamin E.

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1. Introduction

Pathologies affecting the optic nerve and retina are one of the major causes of blindness. These diseases include age-related macular degeneration (AMD), diabetic retinopathy (DR) and glaucoma, among others [1–3]. The prevalence of neurodegenerative diseases of the posterior segment has increased as most of them are related with the elderly [4]. Also, there are genetic disorders that affect the retina causing visual impairment such as retinitis pigmentosa, Leber's congenital amaurosis, Startgaard disease and choroideremia, among others.

There are several clinical issues related to the management of neurodegenerative diseases affecting the retina or surrounding tissues. This is the case of neovascular age related macular degeneration and proliferative retinopathy patients affected that need frequent intravitreal injections of anti-VEGF agents. Also, it is important to notice the poor compliance in the treatment with antihypertensive drugs in glaucoma patients with high intraocular pressure (IOP) values. Neurodegeneration is other important issue as it is present in glaucoma patients with high IOP values with no response to hypotensive therapy and in normotensive subjects.

Delivery of active substances in therapeutic concentrations to the targeted intraocular tissues is restricted by the effective static (corneal layers, sclera, retina, blood aqueous and blood retinal barriers) and dynamic barriers (tear dilution, conjunctival and choroidal blood flow, and lymphatic clearance) as well as efflux pumps that are present in the eye [5] (Fig. 1). Instilled drugs have poor bioavailability in the intraocular tissues [6]. For this reason, the ophthalmic topical administration is restricted to the treatment of pathologies involving the ocular surface or whether the pharmacological target is located in the anterior segment of the eye. Intraocular and periocular injections are used to release therapeutic molecules inside the eye. In the case of intravitreal injections the drug is injected close to the retinal tissues, which leads to the highest bioavailability in the posterior segment tissues compared with the other local routes of administration. Although periocular injections are less invasive, the therapeutic molecule has to reach the posterior segment by diffusion through different tissues.

Intravitreal injections are regularly used in the clinical practice for the treatment of posterior segment diseases. However, even with the available access to different ocular therapies, there are some challenges in the management of patients suffering retinal diseases. One of them is the need of frequent interventions. Also, an unpredictable response to therapy has suggested that different pathways may be playing a role in the development of these diseases. This might the reason why monotherapy is not enough to slow the progression of the degeneration [7].

One of the most challenging areas in ophthalmology therapy is dedicated to decrease the number of interventions. Under the technological

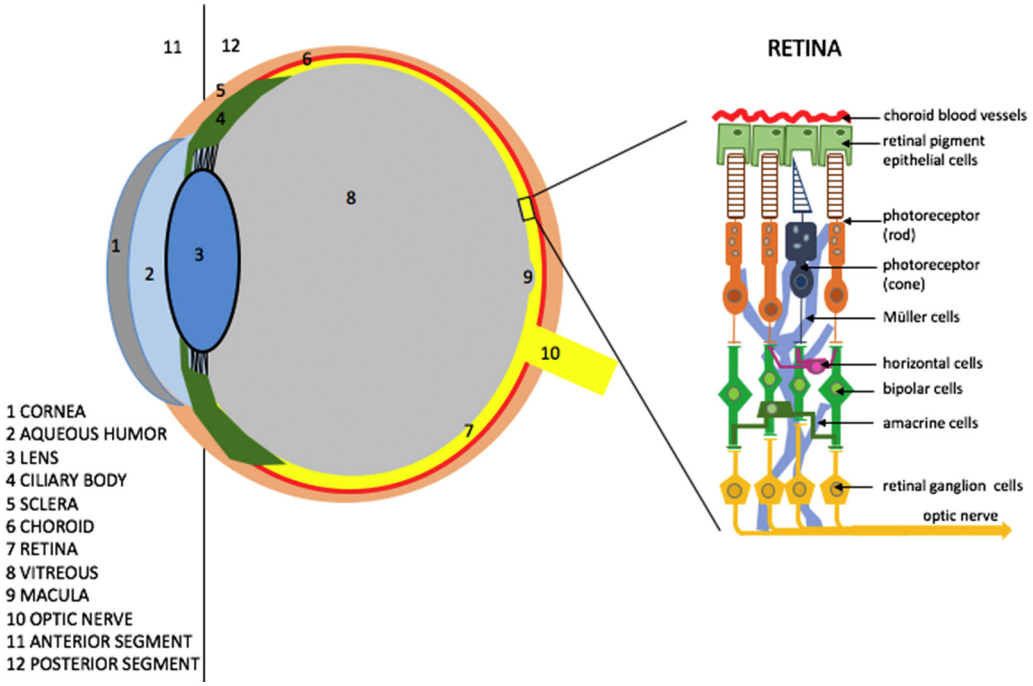

Fig. 1. Eye and retina elementary structure.