

POLYMERIC DELIVERY OF NEUROPROTECTIVE COMPOUNDS TO THE VITREOUS CAVITY: A POTENTIAL TREATMENT FOR GLAUCOMA

LIBERACIÓN DE AGENTES NEUROPROTECTORES EN LA CAVIDAD VÍTREA MEDIANTE POLÍMEROS: UN TRATAMIENTO POTENCIAL PARA EL GLAUCOMA

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The concept of neuroprotection takes its origin from the pioneering work of Rita Levi-Montalcini, whose work in chick dorsal root ganglia resulted in the discovery of the prototypical neurotrophin nerve growth factor (NGF). In the 50+ years since this discovery, the growth factor class has grown to include a wide variety of compounds with the ability to induce neurite outgrowth in injured neurons, or delay the death of these cells. These include other members of the NGF family (neurotrophin-3 and -4/5 (NT-3 and NT-4/5), brain-derived neurotrophic factor (BDNF), the glial-cell line derived neurotrophic factor (GDNF) family (also includes neurturin), as well as the ciliary neurotrophic factor (CNTF) family (also includes leukemia inhibitory factor (LIF)) and others. While the promise of harnessing the potential of growth factors to treat disease has long been appreciated, translating this work from bench to bedside has been slow and frustrating. A fundamental impediment to the application of neuroprotection to the central nervous system (CNS) involves drug delivery. How does one target a drug to a specific compartment, at a controlled dosage, over a long window of time? Advances have recently been made in this area.

Directed delivery of neurotrophins has been attempted previously for amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) (1). These trials, using intrathecal delivery of CNTF or BDNF, encountered difficulties and were halted due to a

number of serious side effects associated with delivery of high concentrations of recombinant growth factors to the cerebrospinal fluid at the level of the lumbar spinal cord with the goal of also treating the brain. The most troubling of these reactions was the sprouting of nerve fibers in the spinal cord, resulting in severe chronic pain in a number of patients. Targeting the desired structure without involving adjacent ones remains a major obstacle to the application of neuroprotective therapies in the CNS. The structural sequestration of the retina inside the eye, however, presents an opportunity for targeted drug delivery not available in other compartments of the CNS. Despite this opportunity, a number of ongoing studies have attempted to deliver bioactive compounds non-invasively through either the cornea or sclera, with limited success. There is a long history of animal studies where intravitreal injections have been used to deliver drugs directly to the retina and optic axons (2). Although intravitreal injection was a technique previously reserved for use in the treatment of endophthalmitis and retinal detachment, more recent developments such as the advent of steroid use in a variety of posterior segment conditions as well as anti-vascular endothelial growth factor (VEGF) therapy in the wet form of age-related macular degeneration (AMD) have led to widespread clinical acceptance of this approach. Importantly, trials for anti-VEGF therapies have involved large numbers of patients and multiple

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intravitreal injections with a low rate of reported complications. Just a few years ago the concept of using repeated intraocular injections in a clinical therapy would have met with strong resistance, but that is not the case today.

Optic neuropathies, including glaucoma, affect at least 65 million people. The specific causal mechanisms underlying the progressive loss of optic axons in these conditions, particularly those forms of glaucoma not associated with elevated intraocular pressure, remain a subject of active investigation. Meanwhile, many patients do not respond to treatments currently available. For these, and indeed for all glaucoma patients, neuroprotection has been proposed as a therapeutic approach that aims to promote survival of retinal ganglion cells (RGCs), rather than addressing the often unknown underlying causes. RGC survival has been demonstrated following a number of interventions including blockade of apoptosis pathways, prevention of glutamate-induced RGC excitotoxicity and administration of various neurotrophins. Although there have been promising results, many such studies evaluated short-term treatments in the setting of rapid RGC degeneration. Effective neuroprotection in the chronic glaucomas will likely require sustained availability of the active agent over the prolonged course of these diseases.

A number of novel methods have now been developed for sustained delivery of therapeutic agents to the vitreous cavity. Viral vectors and neural progenitor cell transplants have effectively increased RGC survival in rodent models and biodegradable polymer microspheres loaded with retinoic acid have protected against proliferative vitreoretinopathy in rabbits. Biodegradable microspheres are an especially attractive drug delivery vehicle for several reasons. They are relatively inert, generally inciting no more than a modest inflammatory response, they can be precisely formulated so as to alter the duration and amount of drug released (3), and they can be reproduced with high consistency and at low cost.

Our group was able to promote long-term retinal RGC survival by injecting slow-release Poly(DL-

lactide-co-glycolide) (PLGA) microspheres containing GDNF into the vitreous of DBA/2J mice, a model of pigment dispersion glaucoma. Mice were injected 2-3 times at two months intervals. Mice receiving treatment showed 3.5 times greater RGC density than untreated mice at 15 months survival ($p < .05$). We concluded that GDNF released from biodegradable microspheres significantly promoted RGC survival in a mouse model of chronic optic axon loss. The fact that some treatments improved long-term neuronal survival highlights the promise of slow release neuroprotection as a treatment modality in glaucoma.

We are now extending this work to a porcine model of optic neuropathy. Our group, as well as another working in Spain, has chosen the pig as the optimal surrogate species for the development of a glaucoma model (4). As the pig eye more closely resembles that of humans, it is predicted that therapeutic regimens developed in the pig will be more easily applied in the clinic. Although there are a number of challenges to overcome, the future for neuroprotection in the retina, as well as other areas of the CNS, is quite bright. The use of slow-release polymeric delivery systems promises to make saving diseased neurons from death a reality not only in animal models, but in patients as well.

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