·Commentary·

Neuroprotection of retinal ganglion cells with GDNF -Loaded biodegradable microspheres in experimental glaucoma

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Abstract

• Glaucoma is the second leading cause of blindness worldwide, and also the most common optic neuropathy. The ultimate cause of vision loss in glaucoma is thought to be retinal ganglion cell (RGC) death. Neuroprotection of RGC is therefore an important goal of glaucoma therapy. Currently, glaucoma treatment relies on pharmacologic or surgical reduction of intraocular pressure (IOP). It is critical to develop treatment approaches that actively prevent the death of RGCs at risk in glaucoma. Neurotrophic factors have the ability to promote the survival and influence the growth of neurons. Neurotrophic factor deprivation has been proposed as one mechanism leading to RGC death in glaucoma. Effective neuroprotection in glaucoma likely requires the consistent availability of the active agent for prolonged periods of time. Biodegradable microspheres are especially attractive as drug delivery vehicles for a number of reasons. Sustained GDNF delivery by biodegradable microspheres offers significant neuroprotection to injured RGC in experimental glaucoma. PLGA microsphere-delivered GDNF represents an important neuroprotective strategy in the treatment of glaucomatous optic neuropathy and provides direction for further investigations of this hypothesis.

• KEYWORDS: glaucoma; neuroprotection; biodegradable microspheres; GDNF

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INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide, and also the most common optic neuropathy, affecting about 60 million people worldwide in its most common forms. This figure is expected to rise to 80 million by 2020 [1-3]. In glaucoma, progressive death of the retinal ganglion cells (RGCs) leads to optic nerve degeneration and vision loss. The ultimate cause of vision loss in glaucoma is thought to be retinal ganglion cell (RGC) death. Neuroprotection of RGC is therefore an important goal of glaucoma therapy. Therefore, a major therapeutic aim is to facilitate the survival of RGCs [4]. Currently, glaucoma treatment relies on pharmacologic or surgical reduction of intraocular pressure (IOP). However, many patients suffer progressive visual field loss despite what appears to be adequate control of IOP, as it does in normal tension glaucoma. For these reasons, it is critical to develop treatment approaches that actively prevent the death of RGCs at risk in glaucoma [5-12]. Recently, Jiang *et al* [13] show in a rat model of glaucoma that Intravitreal injections of GDNF-loaded biodegradable microspheres significantly increased the survival of RGCs and their axons, suggesting that GDNF delivered by PLGA microspheres may be useful as a neuroprotective tool in the treatment of glaucomatous optic neuropathy.

Neurotrophic factors have the ability to promote the survival and influence the growth of neurons. Neurotrophic factor deprivation has been proposed as one mechanism leading to RGC death in glaucoma [14-18]. Retrograde axonal transport of neurotrophic factors synthesized in target structures has been specifically associated with RGC survival. In addition, the growing recognition that glaucoma is a form of optic neuropathy suggests that neuroprotection, *i.e.*, therapy directed at preventing neuronal loss, may represent an efficacious adjunctive therapy in this setting [6]. The neurotrophin (NT) hypothesis proposes that the obstruction of retrograde transport at the optic nerve head results in the deprivation of neurotrophic support to retinal ganglion cells (RGC) leading to apoptotic cell death in glaucoma. An important corollary to this concept is the implication that appropriate enhancement of neurotrophic support will

prolong the survival of injured RGC indefinitely. This hypothesis is, perhaps, the most widely recognized theory to explain RGC loss resulting from exposure of the eye to elevated intraocular pressure (IOP)[19].

Glial-cell-line-derived neurotrophic factor (GDNF) is a 20kDa glycosylated homodimer belonging to the TGF-β super family that was first recognized for its ability to increase the survival of dopaminergic neurons in animal models of Parkinson's disease [20]. Recent work has established that GDNF signals directly through the cell surface receptor GFR-α and indirectly through the transmembrane Ret receptor tyrosine kinase [21]. Both receptors have been identified on embryonic chick RGCs as well as on amacrine and horizontal cells [22]. Exogenous GDNF also increased RGC survival in axotomized rats and in mice following liquid injection and adenoviral transmission [23-26]. Intravitreal microsphere-delivered GDNF significantly increased long-term RGC survival in the DBA/2J mouse glaucoma model[27].

Glaucoma is a chronic disease. Effective neuroprotection in glaucoma likely requires the consistent availability of the active agent, such as GDNF, for prolonged periods of time. Neurotrophic factors present in the vitreous humor are rapidly degraded by free extracellular proteases, including any released as a consequence of RGC degeneration. In addition, neurotrophic factors may be taken up and degraded in the retina by resident microglia. Repeated injections of unprotected neurotrophic factors over the life of the patient might not be sufficient to consistently confer a significant visual advantage and could be expected to result in an unacceptable rate of serious complications such as retinal detachment and endophthalmitis.

Biodegradable microspheres are especially attractive as drug delivery vehicles for a number of reasons. First of all, they are relatively inert in the vitreous cavity, inciting only a minimal host immune response. Furthermore, they can be formulated in ways so as to alter the duration and magnitude of drug release. In addition, they can be reproduced with high consistency and at low cost[27-29].

Recently, Jiang et al. investigated the potential survival enhancing role for glial cell line-derived neurotrophic factor (GDNF) using the hypertonic saline model [13,30]. After showing that biodegradable microspheres persist in the vitreous for at least 6 weeks, they injected GDNF and control microspheres at 1 week after an initial hypertonic saline injection. At 8 weeks following a second hypertonic saline injection, retinas and optic nerves were collected and analyzed by immunohistochemistry and histology. Jiang *et al* [13] showed that the pressure levels rose gradually, stabilizing at 3 weeks at about twice normal values in all experimental groups. Immunolabeling for GDNF and its receptors showed that these proteins were localized, in part, to RGC. In retinas treated with GDNF spheres, the authors reported decreased nerve head cupping, increased nerve fiber layer thickness, significantly increased inner plexiform layer thickness, more importantly, significantly increased RGCs and axonal survival. In addition, retinal glial activation, which has been proposed as an important factor contributing to RGC death in glaucoma [31,32], significantly reduced [13]. These results provide the best evidence so far that sustained GDNF delivery by biodegradable microspheres offers significant neuroprotection to injured RGC in experimental glaucoma. Although these results provide hope for the glaucomatous optic neuropathy, they also have implications for treatment strategies in other retinal degenerative diseases. In summary, these results show that PLGA microsphere-delivered GDNF represents an important neuroprotective strategy in the treatment of glaucomatous optic neuropathy and provides direction for further investigations of this hypothesis.

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