Title: **Neuroprotection of retinal ganglion cells with AAV2-BDNF pretreatment in a microbead trabecular occlusion model of glaucoma: a support to stem-cell based therapy?**

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Abstract:

In models of glaucoma, brain-derived neurotrophic factor (BDNF) therapy can delay or halt RGCs loss, but this protection was found time-limited. The decreased efficacy of BDNF supplementation has been in part attributed to downregulation of its high-affinity receptor, TrkB. However, whether BDNF overexpression causes TrkB downregulation, impairing long-term BDNF signaling in the retina, has not been conclusively proven. We examined quantitatively the retinal concentrations of the TrkB protein in relation to BDNF, in a course of adeno-associated viral vector gene therapy (AAV2-BDNF), using a microbead trabecular occlusion model of glaucoma. We shall report that unilateral glaucoma, with intraocular pressure (IOP) increased for five weeks, leads to a bilateral decrease of BDNF in the retina at six weeks, accompanied by up to four-fold TrkB protein upregulation. On the contrary, a moderate BDNF overexpression evoked by intravitreal delivery of AAV2-BDNF prior to glaucoma triggers changes that restore normal TrkB concentrations, driving signaling towards long-term RGCs neuroprotection. The results suggest that careful control of BDNF concentration is the main factor securing the long-term responsiveness of RGCs and the maintenance of TrkB normal levels. While further studies are required to document time course of changes in neurotrophic signaling in AAV-BDNF pre- and post-treatment paradigms, our results encourage the examination of combinatorial therapy with the use of viral-mediated gene therapy and stem cells.

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