Slow-release intraocular drug delivery by injectable PEA microfibrils

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Purpose

Ophthalmic drug therapy of the posterior segment requires that effective concentrations of drug reach the target tissue, a goal complicated by limited penetration, short half-life of many drugs and difficult access to the posterior segment. Generally drug delivery to the posterior segment of the eye is accomplished by intravitreal (ivt) injection, often requiring frequent injections, e.g., AMD treatment with ranibizumab or aflibercept. Continuous drug delivery systems would be useful to avoid frequent administration and to deliver the drug at a more physiological concentration. Here we report properties of biodegradable amino acid polymer amide (PEA) polymers (PEA III Ac Bz and PEA III 25% X) that can deliver a spectrum of drugs in a sustained manner over long period of time.

Methods

Remodeling and in vitro erosion of the PEA fibrils (4 mm in length and 120-300 µm in diameter) were analyzed by incubation at 37°C in PBS, human, and rabbit vitreous. In vivo biocompatibility and degradation were analyzed by subconjunctival (sc) and ivt implantation in normal and VEGF-treated rabbits. VEGF injection simulates blood-retinal barrier breakdown characteristic for many diseases of the posterior segment. The animals were regularly funduscopically controlled including an intraocular pressure (IOP) measurement. After finalization the ocular tissue was histologically examined. Changes in molecular weight and mass were determined by GPC in THF and weighing. HPLC measurements determined drug release by single PEA and PLGA fibrils loaded with dexamethasone in vitro.

Results

During the first hours of incubation the fibrils decreased in length more than 50% in PBS, rabbit and human vitreous; this decrease in length was accompanied by an increase in diameter. Molecular weight and mass loss after incubation in buffer and after in vivo implantation progressed in a similar way with a detectable mass loss not until after 150 days. After loading of the polymer with dexamethasone a constant release rate of 0.05-1.0 µg/ml for 140 days could be determined, whereas PLGA 75/25 did not release significant amounts of dexamethasone during the first 120 days, followed by 90% release from day 120 to day 140. Remodeling of the fibers in healthy animals after ivt implantation was slight but increased in vitreous from VEGF-treated rabbits after 24 weeks. Both, sc and ivt PEA fibrils were well tolerated with no evidence of inflammation, retinal damage or changes in IOP. 24 h after surgery, 4 and 24 weeks post-OP.

Conclusion

PEA III Ac Bz and PEA III 25% X polymers are well tolerated in the ocular environment. The polymers showed slowly long-lasting mass and weight loss in vitro and in vivo corresponding with remodeling observed during funduscopic control. The polymer can easily be loaded with drugs that are released with nearly zero-order kinetics over a period of months. Since biocompatibility of PEAs is high in the ocular environment in vivo and can be manufactured to be loaded with different classes of drugs, these materials would be ideal for sustained delivery of drugs to the posterior segment.