OBJECTIVE: To investigate the efficacy of two melanocortin agonists in treating mouse models of diabetic retinopathy and CNV.

INTRODUCTION

The melanocortin system plays a key role in the inhibition of leukocyte activation and inflammation. Targeting this pathway can be an alternative to current therapies for specific retinal diseases. Melanocortin agonists have demonstrated anti-inflammatory effects in various experimental models of inflammatory disease. PL8331 and PL9654 are melanocortin 1 receptor agonists being evaluated preclinically for the treatment of various ocular diseases.

METHODS

Study 1: Mice with streptozotocin-induced diabetic retinopathy were given IVT injections of PL8331 at weeks 1, 4, 8, 12, and 16. At week 17, retinas were evaluated for retinal ganglion cell (RGC) density, VEGF expression, and the effects of RPE on macrophage production of TNF and IL-10.

Study 2: After induction of CNV by retinal laser burns, mice were given 1 of 6 treatments by IVT injection. Study 1: Mouse Model of Diabetic Retinopathy

**RESULTS**

Study 1: Mouse Model of Diabetic Retinopathy

Untreated Diabetic Retinas vs. healthy controls showed:

- Reduced RGC density (P ≤ 0.05).
- Increased VEGF concentrations (P < 0.005).

Diabetic retinas treated with PL8331 vs. Untreated Diabetic Retinas:

- Maintained higher RGC density.
- Showed decreased levels of VEGF.
- RPE-promoted macrophage production of the anti-inflammatory cytokine IL-10.

**CONCLUSIONS**

In a mouse model of diabetic retinopathy, monthly IVT treatment with PL8331 preserved retinal structure, suppressed VEGF production, and promoted anti-inflammatory activity.

IVT treatment with the melanocortin agonists PL8331 and PL9654 decreased mean area of leakage, angiogenesis, and fibrosis. These findings support the continued development of both agents for the treatment of retinal diseases.