Targeting plasma kallikrein with a novel bicyclic peptide inhibitor reduces retinal leakage in a diabetic rat model

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DESIGN OF THE STUDY. Therapeutic effect of plasma kallikrein (PKal) inhibition in a diabetic rat model.

PURPOSE. The aim of this study was to test the efficacy of intravitreal (IVT) administration of different doses of THR-149 on retinal vascular leakage in the diabetic streptozotocin (STZ)-induced rat model. THR-149 is a novel potent constrained peptide inhibitor for PKal with high specificity.

METHODS. The *in vivo* efficacy of the PKal inhibitor (THR-149) was tested in the diabetic STZ-induced rat model and compared to anti-VEGF treatment (n=10 rats/group). Administration of 3 repeated IVT injections (with an interval of 1 week between the injections) of THR-149 (1 – 4 – 12.5 µg/eye) or vehicle was started immediately after diabetes onset. Anti-VEGF was administered 3x/week at 2 mg/kg via intraperitoneal injection. Vascular leakage was quantified in all groups at 4 weeks after diabetes onset, by measuring the retinal fluorescence intensity normalized to background intensity after FITC-BSA perfusion.

RESULTS. Retinal vascular permeability was significantly increased (by approximately 2-fold; $p<0.0001$) after STZ-induction of vehicle-treated diabetic rats compared to non-diabetic control rats. Administration of 4 µg/eye and 12.5 µg/eye THR-149 significantly reduced vascular leakage with 25% ($p<0.01$) and 21% ($p<0.01$), respectively, compared to vehicle-treated eyes. This effect was comparable to the effect induced by anti-VEGF treatment (30%, $p<0.001$, as compared to buffer). Administration of 1 µg/eye THR-149 did not induce any significant changes in vascular leakage ($p>0.05$ *vs.* vehicle).

CONCLUSIONS. In this study, it was shown that repeated administration of THR-149, a novel bicyclic peptide, significantly reduced retinal vascular leakage in the diabetic rat STZ model, compared to vehicle-treated eyes. These positive results open perspectives for THR-149 as a possible treatment option for diabetic macular edema (DME).