

# Factor XII contributes to VEGF-induced retinal edema and neuroretinal responses in mice

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# Diabetic Macular Edema (DME)

- DME is a leading cause of vision loss in working aged adults in developed countries
- Anti-VEGF therapies provide incomplete or minimal improvements in visual acuity in ~40% of patients <sup>1</sup>
- Preclinical studies have implicated Plasma Kallikrein as a mediator of both VEGF-dependent and -independent DME <sup>2-7</sup>

1. Gonzalez et al., *Am J Ophthalmol*, 2017, 2. Gao et al, *Nature Medicine* 2007, 3. Phipps et al, *Hypertension* 2009, 4. Clermont et al, *Diabetes* 2011, 5. Liu et al, *IOVS* 2013, 6. Kita et al, *Diabetes* 2015, 7. Clermont et al, *IOVS* 2016

# Clinical Data

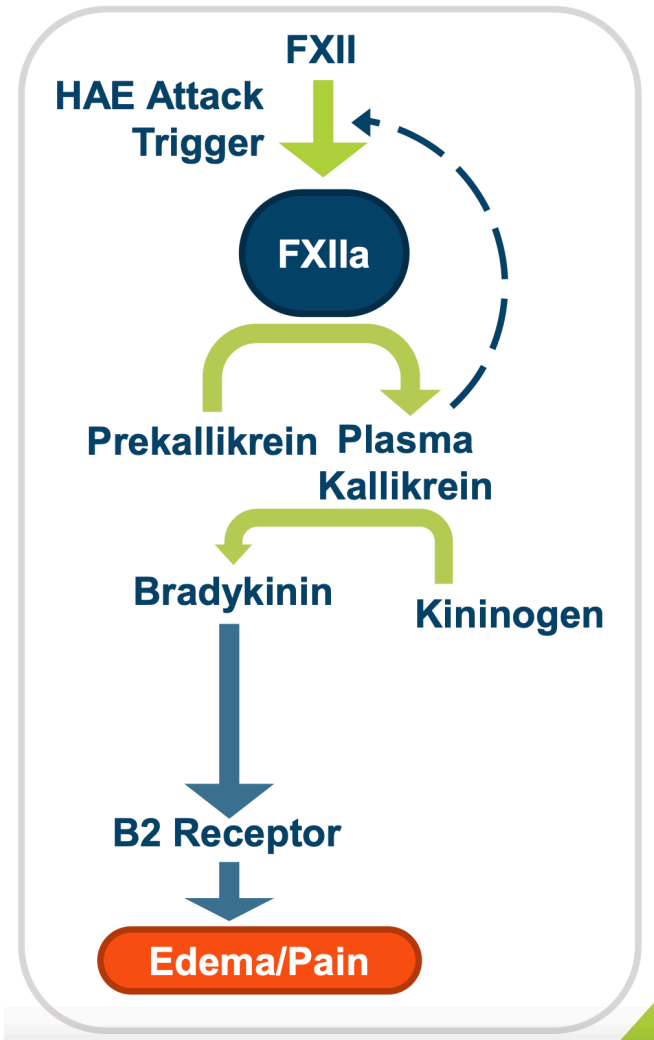
- Plasma kallikrein (PKal) is increased in vitreous of patients with DME compared to subjects with macular hole (MH)<sup>1</sup>.
- A Phase 2 randomized, sham-controlled, double-blind study assessed the efficacy, safety, and tolerability of monthly intravitreal KVD001 (3 or 6 µg) in 129 subjects with ongoing vision loss despite prior anti-VEGF treatment (NCT03466099)
  - Though this study did not meet the primary endpoint (change from baseline in BCVA letter count), it identified trends for improvement in visual acuity
    - At week 16, there was a significant decrease in the proportion of study eyes with any BCVA loss from baseline for KVD001 6 µg (p=0.0421)
    - In subjects with less severe vision loss (BCVA >55 letters), gains in letter score at week 16 favored KVD001 treatment compared to sham (p=0.0561)

<sup>1</sup>Gao, et al *Nat Med* 2007, 13(2), 181-188. Kita, et al *Diabetes*. 2015 Oct;64(10):3588-99

## Factor XII (FXII)

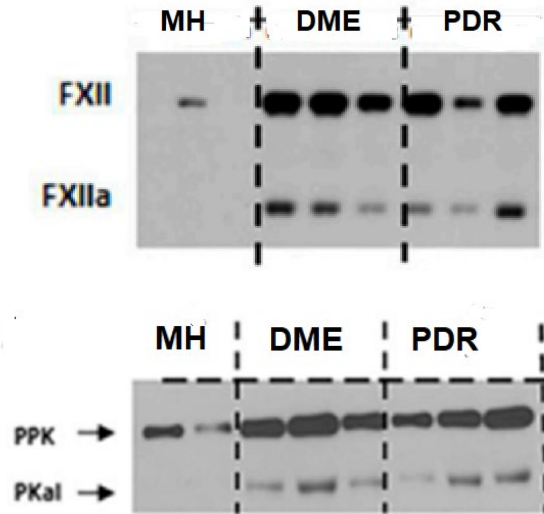
- FXIIa is the primary activator of the kallikrein-kinin system
- Both Plasma kallikrein and FXIIa inhibition reduce attacks in hereditary angioedema<sup>1,2</sup>

<sup>1</sup>Banerji *et al* JAMA 2018, <sup>2</sup>Craig *et al* Lancet 2023



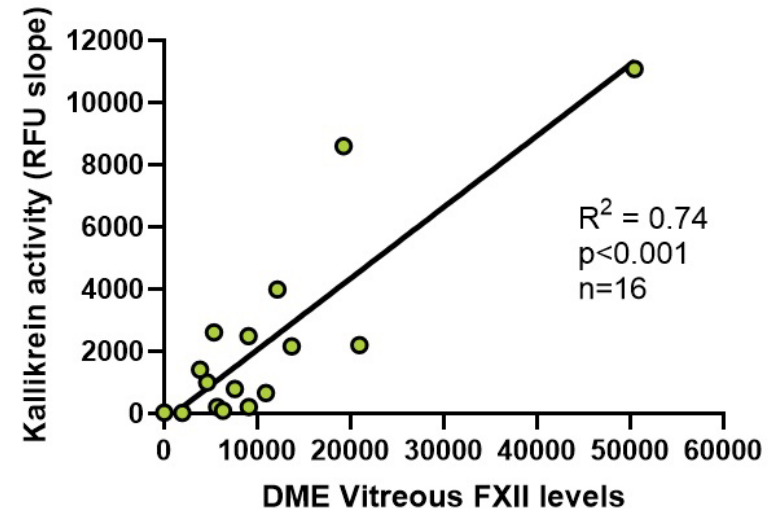
# Factor XII is increased in human DME vitreous

Plasma Kallikrein (PKal) and Factor XII are increased in DME compared with macular hole (MH) vitreous



Source: Kita T et al. Diabetes 2015;64:3588–3599.

FXII protein levels correlate with kallikrein activity in DME vitreous



Source: Ustunkaya T et al. Invest. Ophthalmol. Vis. Sci. 2016;57(12):4183.

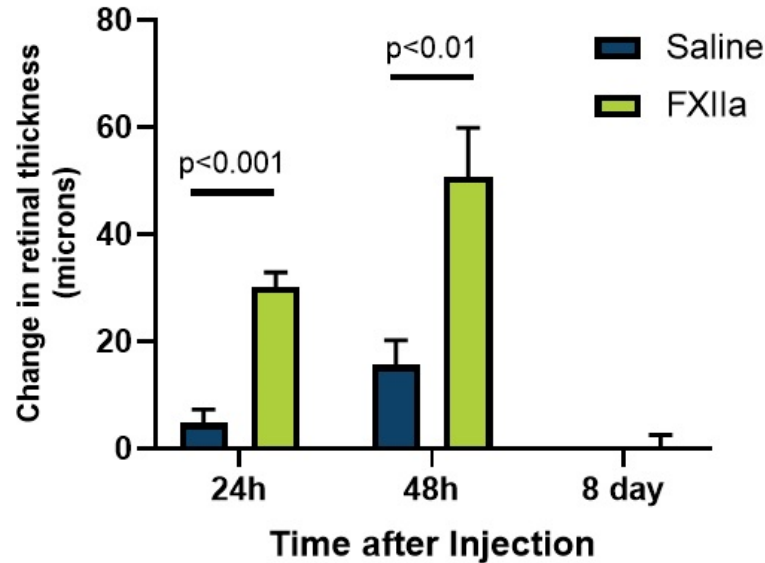
# **Purpose**

**To investigate the effects of FXII  
on retinal edema and neuro-retinal  
responses in mice.**

# Effect of intravitreal FXIIa on retinal thickening

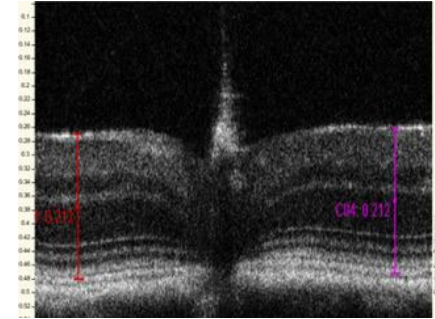
## Method

- Bioptogen Envisu SD-OCT
- C57bL6 mice
- 1uL/eye
- Saline/FXIIa (50ng)

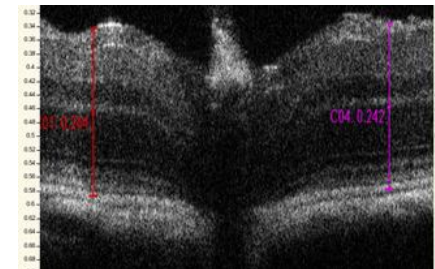


- Intravitreal FXIIa induced a 15% (24h) and 24% (48h) increase in retinal thickening compared with baseline.

Saline (24h)

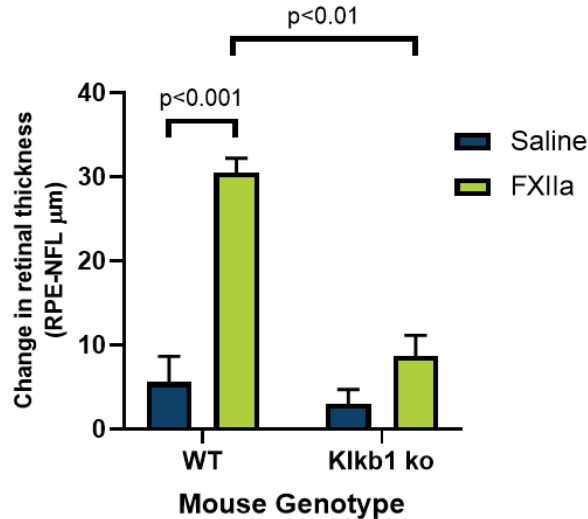


FXIIa(24h)



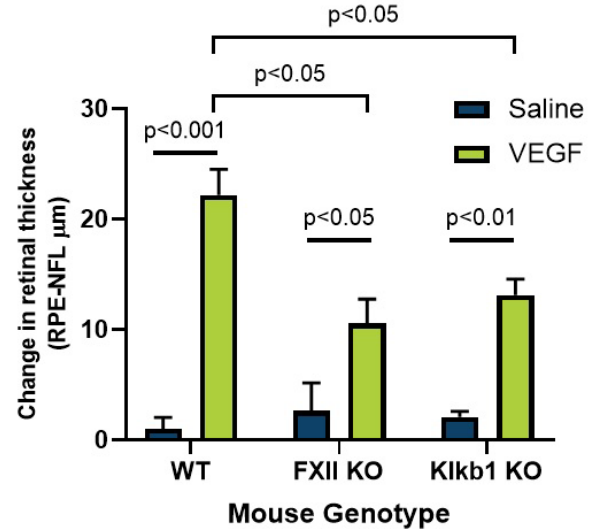
# FXII contributes to VEGF induced retinal thickening

FXIIa in Klkb1 KO



- FXIIa induced thickening is reduced by 77% in plasma prekallikrein (Klkb1) KO mice compared with WT mice

VEGF in FXII KO & Klkb1 KO



- VEGF induced thickening is reduced by 53.1% in FXII KO mice and 41.6% in Klkb1 KO mice compared with WT controls

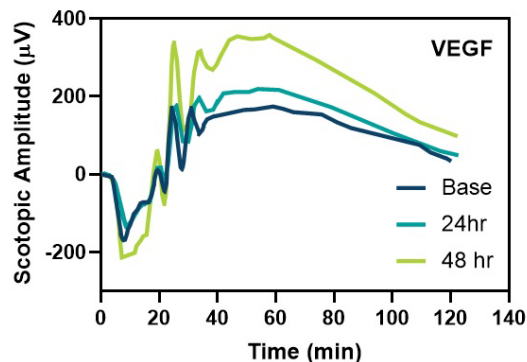
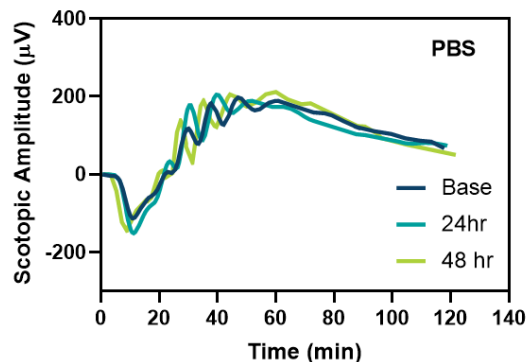


# VEGF stimulates increased ERG amplitude in a time-dependent manner

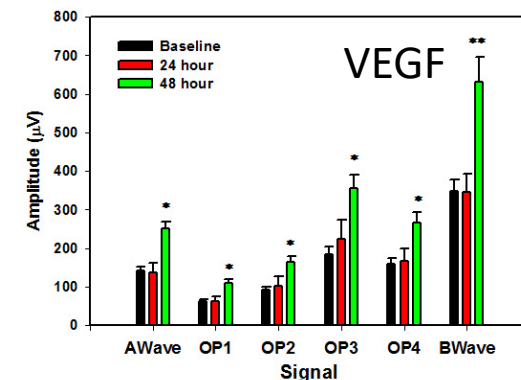
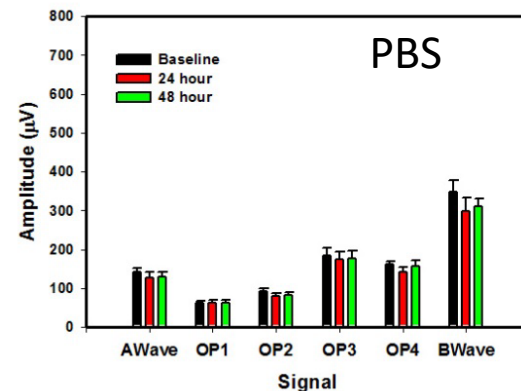
## Method

- SD rat
- VEGF 10ng/eye
- Corneal surface electrode
- Dark adapted overnight
- Maximal stimulation flash
  - 5 ms duration
- Powerlab 4S/Labchart 6

## Scotopic ERG

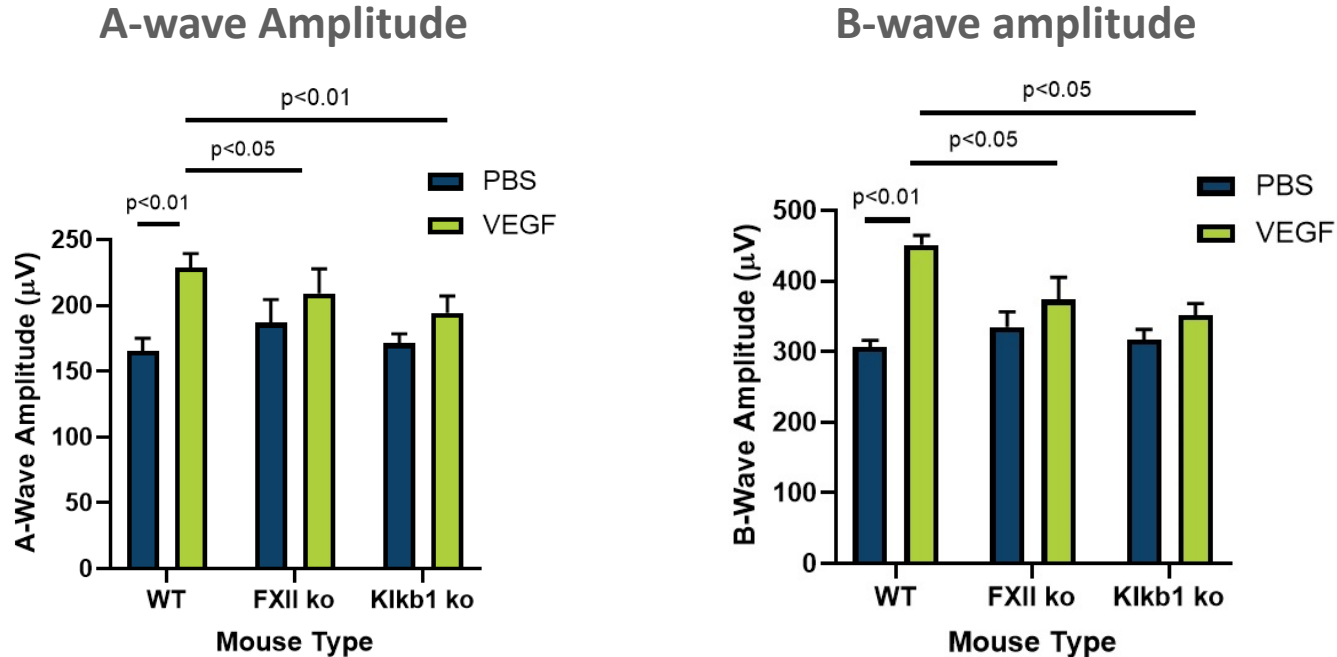


## ERG Amplitude



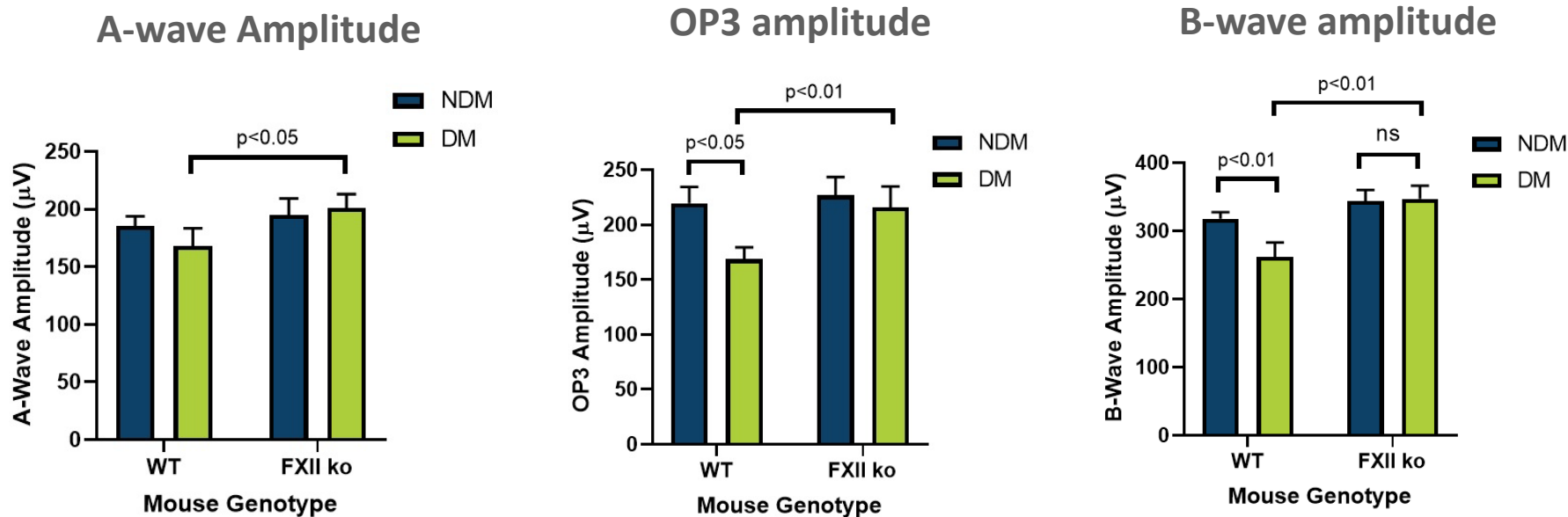
Source: Clermont et al *Invest. Ophthalmol. Vis. Sci.* 2016;57(12)

# VEGF-induced ERG amplitude abnormality is reduced in both FXII and plasma kallikrein knockout mice



- FXII deficiency protects against VEGF-induced neuroretinal dysfunction

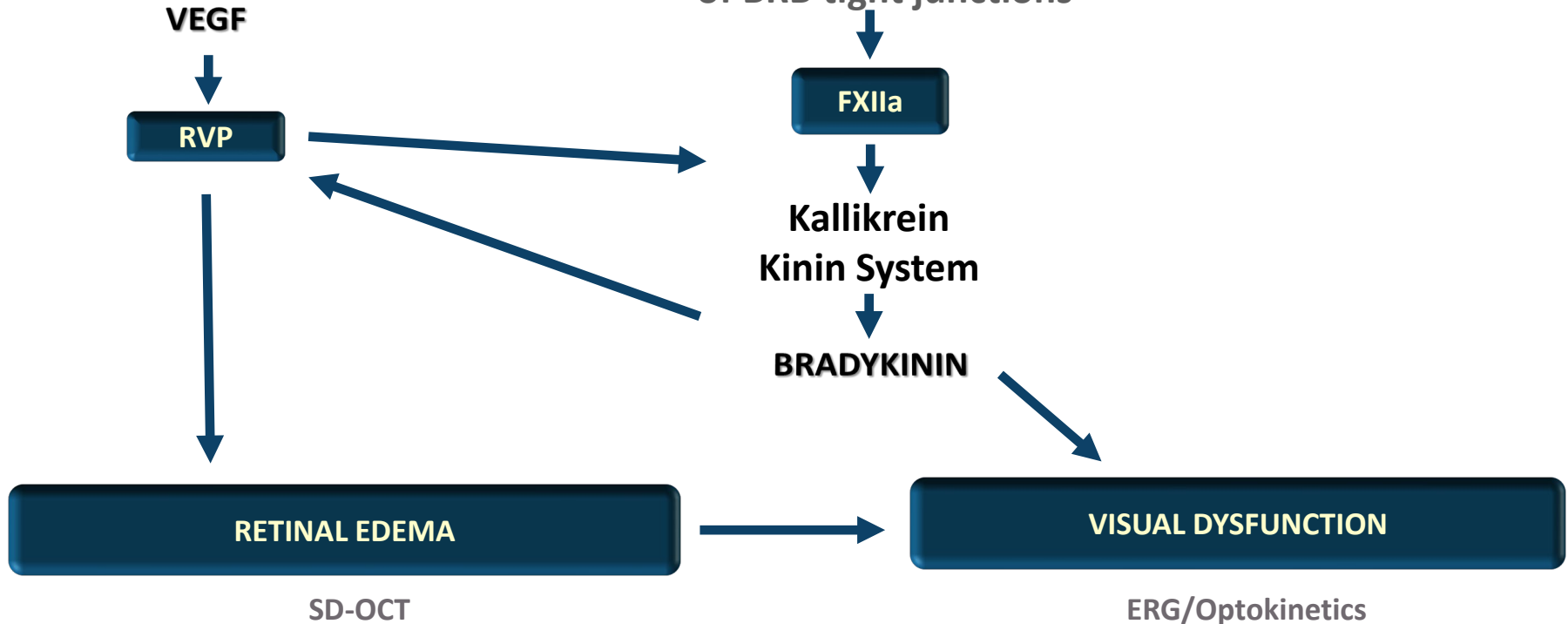
# Effects of FXII deficiency on ERG responses in mice with 4 months of STZ-induced diabetes



- FXII deficiency protects against diabetes-induced neuro-retinal dysfunction

# Potential role of the Kallikrein Kinin System in retinal edema and visual dysfunction

VEGF-independent disruption  
of BRB tight junctions



# Conclusions

- Intravitreal FXIIa induced retinal thickening in WT mice and this effect is mediated through plasma kallikrein.
- Factor XII deficiency reduced VEGF stimulated retinal thickening.
- Factor XII and Plasma kallikrein deficiency are protective against VEGF-mediated and diabetes induced ERG abnormalities.
- FXIIa may provide a therapeutic target for retinal edema and visual dysfunction



**Thank You**