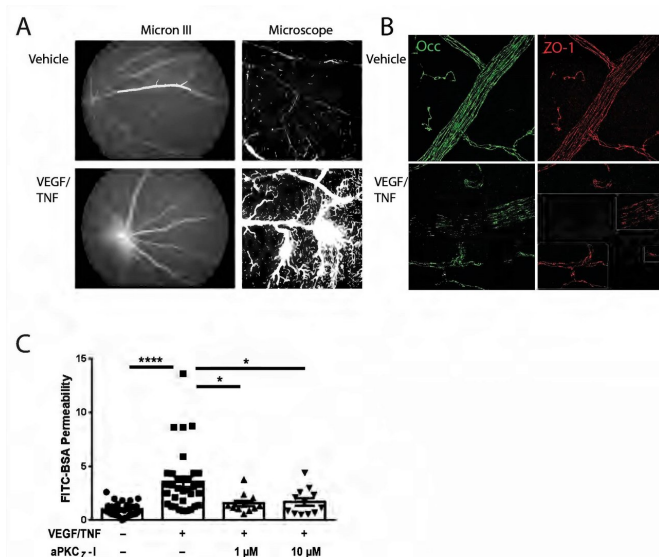


# A potential new way to treat some of the most common blinding diseases

13 September 2018



Vascular endothelial growth factor (VEGF)/tumor necrosis factor (TNF) induces retinal permeability and tight junction loss at the cell border. Rats were injected intravitreally with vehicle [0.1 percent bovine serum albumin (BSA) in phosphate-buffered saline (PBS)] or VEGF/TNF (50/10 ng). A: Fluorescent angiography using Micron III was performed at 5 hours after intravitreal cytokine injection, followed by intravenous injection of fluorescein isothiocyanate--conjugated (FITC) BSA (100 mg/kg body weight) and 10-minute circulation. Generally increased retinal fluorescence, with clear changes at the optic nerve head, is readily observed (Micron III). After angiography, retinas were dissected and flat mounted for microscopic visualization, where vascular leak from capillaries was readily observed (microscope). B: Flat-mount retinas were analyzed for immunoreactivity of occludin (Occ) and zonula occludens protein 1 (ZO-1). Loss of occludin and ZO-1 immunostaining at endothelial cell borders was observed in the VEGF/TNF-treated retinas. C: aPKC  $\gamma$  inhibitor (aPKC  $\gamma$ -I) blocks VEGF/TNF-induced permeability. Rats were intravitreally injected with vehicle (0.1 percent BSA in PBS), VEGF/TNF (50/10 ng), or indicated dose of aPKC  $\gamma$ -I in combination with VEGF/TNF. At 3 hours after intravitreal injection, animals received an i.v. injection of FITC-BSA (100 mg/kg body weight). Two hours later, animals were perfused with warm saline and retinas were removed for quantification

of FITC-BSA accumulation. Results are expressed relative to vehicle control. Differences between groups were analyzed by analysis of variance with Tukey's post hoc test. Data are expressed as means  $\pm$  SEM (C). \*P American Journal of Pathology

Many eye diseases, including diabetic retinopathy and macular degeneration, exhibit increased permeability of blood vessels in the macular (central) portion of the retina leading to abnormal fluid accumulation and vision loss. Therapies targeting a specific cytokine, vascular endothelial growth factor (VEGF), have transformed clinical care; however, not all patients respond well. A new report in *The American Journal of Pathology* shows that inhibiting a specific signaling molecule, atypical protein kinase C (aPKC), either genetically or pharmacologically, reduces increased vessel permeability and blocks inflammation. Blocking aPKC may help protect vision in patients with potentially blinding eye diseases.

"Our data reveal aPKC as an interesting target both for vascular [permeability](#) and inflammation and developing aPKC inhibitors may provide a new therapeutic option for blinding eye diseases," explained lead investigator David A. Antonetti, Ph.D., professor of Ophthalmology and Visual Sciences at The University of Michigan Kellogg Eye Center, Ann Arbor, MI, USA. "Our research may help patients with diabetic retinopathy, the leading cause of blindness in working age adults in the United States, and may also lead to new treatments for uveitis, a spectrum of diseases that leads to inflammation of the eye, as well as for retinal vein and artery occlusions."

Good vision requires retinal neurons to send signals to the brain, and retinal neurons must be protected and kept in a healthy microenvironment within the eye. This microenvironment is maintained, in part, by the selectively permeable

blood-retinal-barrier (BRB). The BRB includes the tight junctions between the endothelial cells of the blood vessels that help control entry of water, nutrients, and ions to the retina. However, injury or chronic disease can weaken the BRB and increase vascular permeability by altering these endothelial tight junctions. Studies have shown that a variety of molecular factors can affect permeability, including growth factor VEGF and the inflammatory cytokine tumor necrosis factor alpha (TNF $\alpha$ ). Although VEGF and TNF $\alpha$  possess distinct signaling mechanisms, both eventually activate a common pathway, aPKC signaling, to change the permeability of the endothelial cells of [blood vessels](#).

Further, aPKC promotes inflammation. In this study, investigators demonstrated the effects of VEGF and TNF $\alpha$  on retinal vascular permeability and the protective effect of an experimental small-molecule aPKC inhibitor using genetic mouse models and novel small molecule inhibitors to aPKC. The investigators also demonstrate the effect of targeting aPKC in a separate model of retinal inflammation. In both models, the genetic as well as therapeutic intervention reduced the vascular permeability and inflammation.

"This study evaluates the therapeutic potential of aPKC inhibition in retinal [vascular permeability](#) driven by inflammation and demonstrates that small molecule aPKC inhibitors have therapeutic potential for common ocular diseases," commented Elizabeth A. Pearsall, Ph.D., Angiogenesis Laboratory of the Department of Ophthalmology at the Massachusetts Eye and Ear Hospital of Harvard Medical School, Boston, MA, USA. in an accompanying [commentary](#). She noted that although there are still many unresolved questions about the etiology of [inflammation](#), and whether it has a causative role in [eye disease](#), additional pre-clinical studies necessary to bring small molecule aPKC inhibitors into clinical use are eagerly anticipated.

The recent advent of drug delivery to the eye provides an exciting opportunity to protect vision. The importance of good vision combined with the ability to deliver a drug in a focused and contained environment in the eye have led to the prospects of

increasing therapeutic options to help individuals suffering from vision loss.

**More information:** "Inhibition of Atypical Protein Kinase C Reduces Inflammation-Induced Retinal Vascular Permeability," *American Journal of Pathology* (2018). DOI: [10.1016/j.ajpath.2018.06.020](https://doi.org/10.1016/j.ajpath.2018.06.020)

Provided by Elsevier

APA citation: A potential new way to treat some of the most common blinding diseases (2018, September 13) retrieved 29 November 2022 from <https://medicalxpress.com/news/2018-09-potential-common-diseases.html>

*This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.*