Study finds novel therapy that may prevent damage to the retina in diabetic eye diseases

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Researchers at the University of Michigan Kellogg Eye Center have identified a compound that could interrupt the chain of events that cause damage to the retina in diabetic retinopathy. The finding is significant because it could lead to a novel therapy that targets two mechanisms at the root of the disease: inflammation and the weakening of the blood barrier that protects the retina.

To date, treatments for diabetic retinopathy, the leading cause of blindness among working-age Americans, have been aimed largely at one of those mechanisms.

In diabetic retinopathy, damage to the retina results, in part, from the activity of vascular endothelial growth factor (VEGF), a protein that weakens the protective blood-retinal barrier. Recent drugs targeting VEGF have exhibited good response for nearly half of the patients with diabetic retinopathy. But researchers believe that there is also an inflammatory component that may contribute to the disease process.

The study, published in the Biochemical Journal, June 2012 [epub ahead of print] identifies a specific protein common to both pathways as an important target in regulating the disease process in which blood vessels become leaky, and provides a drug that may be developed into a therapeutic intervention for patients in which anti-VEGF treatment alone is not sufficient.

"In diabetic retinopathy and a host of other retinal diseases, increases in

VEGF and inflammatory factors — some of the same factors that contribute to the response to an infection — cause blood vessels in the eye to leak which, in turn, results in a buildup of fluid in the neural tissue of the retina," says David A. Antonetti, Ph.D., Professor, Department of Ophthalmology and Visual Sciences and Molecular and Integrative Physiology, who has also been awarded a Jules and Doris Stein Professorship from Research to Prevent Blindness. "This insidious form of modified inflammation can eventually lead to blindness."

The compound targets atypical protein kinase C (aPKC), required for VEGF to make blood vessels leak. Moreover, Antonetti's laboratory has demonstrated that the compound is effective at blocking damage from tumor necrosis factor also elevated in diabetic retinopathy that comprises part of the inflammation. Benefits of this compound could extend to therapies for uveitis, or changes to the brain blood vessels in the presence of brain tumors or stroke.

"This is a great leap forward," says Antonetti. "We've identified an important target in regulating blood vessel leakage in the eye and we have a therapy that works in animal models. Our research is in the early stages of development. We still have a long way to go to demonstrate effectiveness of this compound in humans to create a new therapy but the results are very promising."

More information: Novel Atypical PKC Inhibitors Prevent Vascular Endothelial Growth Factor-Induced Blood-Retinal Barrier Dysfunction, *Biochemical Journal*, 22 June 2012 [epub ahead of print]

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