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Highlights From the Latest in Diabetes Research

Atypical PKC Inhibitors: A Novel Approach to Treat Retinal Diseases

Proper function of tight junctions (TJs) in the vascular endothelium of the blood-retinal barrier (BRB) is required to ensure appropriate neuronal activity. Growth factors and inflammatory cytokines, such as vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α), have been implicated in compromising TJ in the BRB. Tight junction dysfunction leads to vessel hyperpermeability and loss of neural function, which, in turn, are associated with retinal pathologies, including diabetic macular edema (DME). Although antibodies against VEGF have shown some promise in treatment of DME, research suggests that alternate therapies targeting downstream components of the VEGF pathway may be more beneficial in treatment of retinal diseases involving the BRB. Inhibition of protein kinase C-β (PKCβ), a classical PKC isoform, was an initial target for diabetic retinopathy, as VEGF's actions through PKCβ result in TJ breaks. However, classical PKC inhibitors only partially prevented VEGF-induced BRB TJ dysfunction and permeability, and they failed to prevent TNF-α–induced permeability. Titchenell et al. recently investigated the ability of atypical PKC isoform (aPKCζ/aPKCι) inhibitors to prevent VEGF-induced TJ dysfunction. First, the laboratory demonstrated that aPKCs were activated in VEGF-injected rat retinas, and they contributed to VEGF-induced permeability in primary bovine retinal endothelial cells (BRECs). The investigators then developed novel, small molecule inhibitors of aPKC that prevented VEGF-induced permeability in vitro (BREC) and in vivo (rat retina). Studies in BREC demonstrated that aPKC inhibitors prevented VEGF-induced TJ protein disorganization, thus preventing TJ breaks in the endothelial layer. In addition, rat retinal flat mounts were prepared to determine the effect of aPKC inhibitors on the retinal vasculature TJ complex. These experiments showed that aPKC inhibitors prevented VEGF-induced disruption of occludin staining. Previous work from this laboratory demonstrated that aPKC inhibitors blocked TNF-α–induced permeability, providing evidence for the ability of these inhibitors to prevent retinal disease from both growth factor and inflammatory mediators. Another promising element of this novel mechanism is the lack of endothelial cell toxicity or retinal defects. The authors suggest further development of aPKC inhibitor compounds to fully evaluate their benefits in retinal diseases, as well as in blood-brain barrier dysfunctions. — *Eileen M. Resnick, PhD*

■ Titchenell et al. Novel atypical PKC inhibitors prevent vascular endothelial growth factor-induced blood-retinal barrier dysfunction. Biochem J 2012;446:455–467

Potential Value in Computerized Threshold Perimetry as an Outcome in Studies of Diabetic Retinopathy

Diabetes has multiple, unfavorable effects on the eye. Efforts to develop and test new treatment modalities rely on choosing appropriate end points for use in clinical trials. Historically, progression of diabetic retinopathy, as measured by changes in fundus photography, is a common and clinically relevant outcome in clinical trials of diabetic eye disease. However, this outcome does not reflect visual function—an outcome that both the National Institutes of Health and the U.S. Food and Drug Administration have recommended as end points in future clinical trials. Although visual acuity is a functional outcome, using this measure in clinical trials is not practical in the early stages of diabetic retinopathy because edema of the macula is often not present, resulting in limited decrements in this measure. Computerized threshold perimetry is another approach to assessing visual function. This psychophysical method measures light sensitivity, reflects retinal function, and may offer a new strategy to define outcomes in clinical trials because it may be able to detect retinal changes early in the course of diabetes. A recent study by Hellgren et al. addresses these important questions by following a cohort of diabetic patients who were enrolled in an observational study following diabetic retinopathy screening. The 81 patients enrolled in the study had a mean age of 44 years, and 13 had type 1 diabetes. These patients underwent fundus photography as well as perimetry measures on 54 points on the retina. Data in the newly published report contrast these two sets of parallel measures and cover the first 18 months of follow-up. At month 18, fundus photos showed that retinopathy progressed one step in seven eyes and two steps in two eyes and that regression of one step occurred in six eyes. This method indicated that retinopathy, as conventionally defined, did not change in 61 eyes (88%). In contrast, perimetry measures in the same patients showed significant deterioration of ≥5 test points in 38 eyes (50%), and almost no improvement was observed. These preliminary data suggest that among patients with diabetic retinopathy, perimetry measures are not correlated with fundus photo assessments but may reveal defects in the neurosensory retina. These results also raise the possibility that perimetry may be a promising strategy for defining clinical end points in future clinical trials of diabetic retinopathy. — *Helaine E. Resnick, PhD, MPH*

■ Hellgren et al. Functional and structural change in diabetic eyes. Interim results from an ongoing longitudinal prospective study. Acta Ophthalmol. 1 October 2012 [Epub ahead of print]

A New Multifunctional, Conjugate Therapy Combats the Metabolic Syndrome

Treatment of type 2 diabetes often requires a combination of pharmacotherapeutic approaches to target both insulin resistance and insulin deficiency. Although combination therapies show some promise, there are considerable challenges associated with matching drug potencies and gaining regulatory approvals. In addition, effective therapies for weight loss and diabetes prevention are currently lacking. Finan et al. recently developed a unique polypharmaceutical approach that utilizes a covalently conjugated glucagon-like peptide-1 (GLP-1) and the steroid hormone estrogen into one multifunctional, small molecule. GLP-1 is a gut-derived hormone that targets GLP-1 receptor (GLP-1r) expressing tissues, specifically the endocrine pancreas and metabolic control centers in the central nervous system (CNS). GLP-1 has incretin and satiety effects, and GLP-1 analogs have been shown to improve glycemic control, causing modest weight loss. Estrogen has been shown to have a positive impact on metabolism, energy expenditure, and feeding behavior through its leptin-like actions in the hypothalamus, making it a candidate therapy for obesity and type 2 diabetes. However, its clinical application has been limited because of potential harmful reproductive and tumor-promoting effects. The Finan laboratory's GLP-1 conjugate chaperoned estrogen specifically to GLP-1r expressing brain cells, resulting in synergistic, biological actions through both GLP-1r and estrogen receptors (ERs) α and β, and these effects occurred without estrogen's unfavorable systemic effects (uterine hypertrophy and tumor growth). In diet-induced obese (DIO) male mice, the GLP-1/estrogen conjugate lowered body weight by 23.8% compared to 10.3% with GLP-1 alone, and similar results were observed in female mice. The GLP-1 conjugate also improved several metabolic factors including hyperglycemia, glycemic control, insulin sensitivity, and dyslipidemia. Additional studies using CNS-specific GLP-1r knockout mice demonstrated that the GLP-1/estrogen effects on body weight resulted from actions through the GLP-1r in the hypothalamus. These experiments also showed selective activation of ERs in the brain, but not liver, of DIO mice due to the GLP-1/estrogen conjugate's ability to selectively target specific tissues. Further, knockout studies of the individual ERα and ERβ isoforms demonstrated that both ERs were required for the weight-lowering effects of the GLP-1/estrogen conjugate. This novel approach, which joins a specific cell-targeting peptide with a small molecule and leads to synergistic metabolic benefits, may be a powerful therapeutic approach for metabolic disorders. — *Eileen M. Resnick, PhD*

■ Finan et al. Targeted estrogen delivery reverses the metabolic syndrome. Nat Med 2012;18:1847–1856

Questions Raised About the Timing of Grid Laser Treatment Among Patients With Diabetic Macular Edema Treated With Ranibizumab

Macular edema is the most common cause of vision loss among people with diabetes. Given the disability associated with vision loss, coupled with the high prevalence of diabetes, there is interest in identifying optimal treatment regimens for individuals with diabetic macular edema (DME). New data published in *Ophthalmology* summarize follow-up of an ongoing cohort study of DME patients and provide insight into a common combination therapy. In this study, all patients received intravitreal 0.5 mg ranibizumab and were randomly assigned to receive focal/grid laser treatment at initiation of ranibizumab (prompt laser treatment; n = 144) or to receive this treatment ≥24 weeks after initiation of ranibizumab (deferred laser treatment; n = 147). Ranibizumab was administered every 4 weeks until patients no longer improved, and treatment could be resumed if patients worsened. The primary outcome was best-corrected visual acuity at the 3-year visit. At that time, there was a 2.9-letter difference in visual acuity between the groups, with the deferred laser group having more favorable scores. Moreover, after week 68 of follow-up, visual acuity in the prompt laser group appeared to diminish somewhat, while visual acuity in the deferred laser group continued to improve. Further, a significantly higher proportion of patients in the deferred laser group had a ≥10-letter improvement during follow-up. However, optical coherence tomography data describing central subfield retinal thickening did not indicate any differences between the groups. Notably, the median numbers of cumulative injections in the prompt and deferred groups were 12 and 15, respectively, and no differences in adverse events were noted. Data from extended follow-up of this cohort suggest that among DME patients, focal/grid laser treatment may be more effective if it occurs ≥24 weeks after initiation of ranibizumab. However, these findings may be related in part to differences in the number of ranibizumab injections that were received in the two study groups. — *Helaine E. Resnick, PhD, MPH*

■ Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology 2012;119:2312–2318

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