Progressive Early Breakdown of Retinal Pigment Epithelium Function in Hyperglycemic Rats

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PURPOSE. Diabetic macular edema (DME), an accumulation of fluid in the subretinal space, is a significant cause of vision loss. The impact of diabetes on the breakdown of the inner blood-retina barrier (BRB) is an established event that leads to DME. However, the role of the outer BRB in ocular diabetes has received limited attention. We present evidence that the breakdown of normal RPE function in hyperglycemia facilitates conditions conducive to DME pathogenesis.

METHODS. Brown Norway rats (130–150 g) were injected intraperitoneally with streptozotocin (STZ; 60 mg/kg) to induce hyperglycemia. After 4 weeks, Evans blue (EB) dye was injected intravenously to determine whether there was leakage of albumin into the retina. Subretinal saline blebs (0.5–1 μL) were placed 4 and 9 weeks after STZ injection, and time-lapse optical coherence tomography tracked the resorption rate. In a subset of rats, intravitreal bevacizumab, a humanized monoclonal antibody targeted to VEGF, was given at 5 weeks and resorption was measured at 9 weeks.

RESULTS. The ability of the RPE to transport fluid was reduced significantly after 4 and 9 weeks of hyperglycemia with a reduction of over 67% at 9 weeks. No EB dye leakage from inner retinal vessels was measured in hyperglycemic animals compared to control. The intravitreal administration of bevacizumab at week 5 significantly increased the rate of fluid transport in rats subjected to hyperglycemia for 9 weeks.

CONCLUSIONS. These results demonstrate that chronic hyperglycemia altered RPE fluid transport, in part dependent on the actions of VEGF. These results support the idea that RPE dysfunction is an early event associated with hyperglycemia that contributes to fluid accumulation in DME.

Keywords: RPE, DME, hyperglycemia, diabetes, VEGF

Loss of vision is of significant cost to the quality of life and productivity in patients with diabetic retinopathy (DR). There are over 128 million diabetics worldwide and approximately 28% of those patients have some symptoms of DR, while a further 4.4% live with vision-threatening DR. Diabetic macular edema (DME) is one manifestation of DR and the most frequent cause of vision loss among diabetic working-age adults in the developed world. In DME, extracellular fluid accumulates within the layers of the neural retina, threatening the supply of nutrients and exchange of waste between the photoreceptors and the RPE. The resulting disruption of communication between the photoreceptors and blood supply leads to a loss of visual acuity, and if the disease persists, to eventual blindness. The consequences of DME often are more severe than other forms of DR because the location of the disease lesion is the macula, the area of the retina responsible for high-acuity daylight color vision. Compounding the situation, a new insulin regimen in patients previously on oral medications often leads to a worsening of DME symptoms.

Maintenance of the two blood retinal barriers (BRBs) is essential for retina homeostasis and disruption of one or both of the BRBs can result in fluid accumulation in the subretinal space. The inner BRB is formed by tight junctions between the endothelial cells of the inner retinal vessels. The outer BRB is made up of tight junctions between adjacent RPE cells, separating the neural retina from the choroid. In addition to forming a passive barrier, the RPE is also responsible for active fluid resorption from the retina. The rupture of the inner BRB by VEGF most often is cited as the source of fluid leakage in the diabetic neuroretina; however, several recent studies indicate that the breakdown of the RPE barrier could have an equally detrimental role in the pathogenesis of DR.

Vascular endothelial growth factor has a vital role in the pathogenesis of DME, and anti-VEGF agents are used in the clinics to treat the condition. Our laboratory recently has developed a new method to assess RPE fluid transport in rabbits, allowing the assessment of RPE responses to subretinally-injected VEGF and following 48-hour incubation with intravitreally-injected glycated-albumin. In both of these acute rabbit models, we found a dramatic reduction in bleb resorption rates.

Although the use of rabbits is preferential for isolating RPE function from any influence of the inner retina vasculature, the avascular rabbit retina is far removed from human ocular anatomy. Therefore, to demonstrate a direct link between hyperglycemia, the functional deficiency of the RPE, and the...
development of DME, we chose to use streptozotocin (STZ)-induced hyperglycemic diabetic rats that are a better model of human diabetes. The results presented in this manuscript provide evidence that in hyperglycemic Brown Norway rats, RPE fluid transport is reduced significantly at 4 and 9 weeks after STZ injection. In this model, RPE dysfunction is apparent early in the course of chronic systemic hyperglycemia and mediated at least in part by the endogenous release of VEGF.

METHODS

Animals

Common Procedures. Brown Norway rats (Jackson Laboratories, Bar Harbor, ME, USA) weighing 130 to 150 g were anesthetized using intraperitoneal ketamine (20 mg/kg) and xylazine (2 mg/kg; both from Butler Schein, Columbus, OH, USA), with additional aliquots administered as needed during extended experiments. The pupils were dilated using 10% phenylephrine hydrochloride (Bausch & Lomb, Tampa, FL, USA) and atropine (Bausch & Lomb) drops, administered topically. For local anesthesia, proparacaine, 5% iodine solution was used to sterilize the sclera. A 26-gauge needle was inserted 1 to 2 mm posterior to the limbus and a 35-gauge blunt needle was used to introduce the opening in the sclera under the conjunctiva. Infrared fundus images and OCT tomographs of each eye were performed using an injection of sterile PBS into the sub-RPE space, 0.5 to 2 μL of sterilized PBS was injected gently to produce a bleb. Infrared fundus images and OCT tomographs (transverse and sagittal planes), as well as full volume scans were taken every minute for the first 5 minutes after injection and compared for evidence of leakage. Animal handling was performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and the study protocol was approved by the Animal Care and Use Committee at the Medical University of South Carolina.

Hyperglycemic Animals. Brown Norway rats were injected intraperitoneally with streptozotocin (60 mg/kg dissolved in sterile citrate buffer at 10 mg/mL, pH 4.5) and housed with 10% sucrose water ad libitum for 24 hours. Dose-dependent retinal and systemic toxicity of STZ was assessed previously.12,13 Only confluent monolayer cultures with stable TEER values (40–50 Ωcm²) were used in the experiments. Rats were killed with Fatal Plus (Vortech Pharmaceuticals, Ltd., Draper, UT, USA) and the retina was calculated using a standard curve.

RPE Fluid Transport

Optical Coherence Tomography (OCT). One subretinal bleb per eye was generated using an injection of sterile PBS with methods similar to those reported previously.10,19 In short, after systemic anesthesia with 50/50 ketamine/xylazine and local anesthesia with proparacaine, 5% iodine solution was used to sterilize the sclera. A 26-gauge needle was inserted 1 to 2 mm posterior to the limbus and a 35-gauge blunt needle was advanced through the opening in the sclera under the guidance of a Spectralis OCT instrument (Heidelberg Engineering, Heidelberg, Germany). Upon reaching the sub-retinal space, 0.5 to 2 μL of sterilized PBS was injected gently to produce a bleb. Infrared fundus images and OCT tomographs (transverse and sagittal planes), as well as full volume scans were taken every minute for the course of 20 to 30 minutes using the OCT instrument. Rates of bleb resorption were calculated using Prism 6 (Graphpad Software, Inc., La Jolla, CA, USA) and Microsoft Excel (Microsoft, Redmond, WA, USA) software using linear regression analysis of the changes in bleb volume, as described previously.19 Anti-VEGF Treatment. Rats at 5 weeks after STZ induction were anesthetized as described above, and the humanized monoclonal antibody against VEGF, bevacizumab (1 μL of a 1.25 mg/50 μL solution in PBS; from Genentech, San Francisco, CA, USA), was injected intravitreally. Specifically, the sclera was punctured using a 26-gauge needle approximately 1 mm posterior to the limbus and a 30-gauge needle was inserted to inject the bevacizumab solution into the vitreous. Animals injected with sterile saline served as controls.

Fluid Leakage

Fluorescein Angiography. Rats were injected intraperitoneally (IP) with 60 mg/kg fluorescein dissolved in sterile saline (100 mg/mL) and imaged using the Spectralis OCT instrument. Images were collected every minute for the first 5 minutes after injection and compared for evidence of leakage. Evans Blue Assays. Evans blue (EB) dye covalently links to albumin and serves as a sensitive indicator of albumin leakage into the retina from the vasculature.20,21 Evans blue dye was injected intravenously (30 mg/mL; 30 mg/kg) through the femoral vein of the rats. After 1 hour, rats were killed and the neural retina was removed and weighed. Retinas were incubated with formamide (120 μL) for 18 hours at 70°C, and then were centrifuged for 70 minutes, 14,000 rpm at 4°C. For positive control rats, after anesthesia, eyes were injected with 1 μL VEGF-E 1 hour before EB injection; animals remained anesthetized for the remainder of the experiment. Absorbance of each sample was read in duplicate at 620 nm and EB content in the retina was calculated using a standard curve.

Tissue Culture

Common Procedures. We obtained ARPE19 cells from the American Type Culture Collection (Manassas, VA, USA). Confluent monolayers were established and maintained on permeable membrane inserts and transepithelial electrical resistance (TEER) measurements were assessed as described previously.12,13 Only confluent monolayer cultures with stable TEER values (40–50 Ωcm²) were used in the experiments. Treatments. Cultures were treated apically with 100 ng/mL of rat VEGF (PeproTech, Rocky Hill, NJ, USA) diluted in PBS. Change in TEER was followed at the time of administration and for 6 hours after VEGF administration. In selected experiments, the anti-VEGF humanized antibody bevacizumab (1.25 mg/mL) was added apically to the cells 10 min before rat VEGF.

Immunoblotting

Recombinant human VEGF (ThermoFisher Scientific, Waltham, MA, USA) and rat VEGF were resuspended in PBS and serially diluted. One microliter of solution was blotted on nitrocellulose membrane, blocked with Super Block (ScyTek Laboratories, Logan, UT, USA), and incubated with bevacizumab (250 μg/mL). After washing the membrane with Tris-buffered saline, the membrane was incubated with a goat anti-human IgG horseradish peroxidase conjugated antibody (1:5000; Thermo Fisher Scientific). The blot then was incubated with SuperSignal West Femto Maximum Sensitivity Substrate (Thermo Fisher Scientific) and imaged.

Immunohistochemistry

Rats were killed with Fatal Plus (Vortech Pharmaceuticals, Ltd., Dearborn, MI, USA), eyes were enucleated and fixed in ice-cold 4% paraformaldehyde for 30 minutes to fix the sclera, and the cornea was then punctured and fixed for an additional 2 hours on ice. Eyes then were washed with PBS. Flat mounts were permeabilized and blocked with 3% BSA, 5% normal goat serum, and 0.3% Triton X-100 in PBS for 1 hour at room temperature. Fluorescein isothiocyanate–conjugated ZO1 primary antibody (1:200; ThermoFisher Scientific) was added to permeabilization buffer and incubated overnight at 4°C. Flat mounts were washed with PBS, mounted, and visualized on a
Zeiss LSM 880 NLO confocal microscope (Carl Zeiss, Jena, Germany) and processed using the public domain Fiji Software.

**Statistical Analysis**

All values represent a mean of at least 6 independent experiments ± SEM. Pairwise data were analyzed using Student’s t-test and were considered statistically significant at \( P < 0.05 \). Where multiple comparisons were required, results were compared with 1-way ANOVA, Bartlett’s post-test (\( \alpha = 0.05 \)) using Prism 6 (Graphpad Software, Inc.).

**RESULTS**

**Lack of Vascular Leakage After 4 and 9 Weeks of Hyperglycemia**

Rats were injected once with STZ (60 mg/kg) to lyse pancreatic \( \beta \) cells, resulting in insulin deficiency. At 1, 4, and 9 weeks after STZ injection, weight and plasma glucose levels were measured and compared to baseline measurements. At 1 week after STZ injection, average glucose levels were 347.12 ± 16.48 mg/dL, while age-matched control rats had plasma glucose levels within normal limits (85.95 ± 3.31 mg/dL; Fig. 1). These levels were maintained throughout the duration of the study.

Weights were measured to assess the overall health of the animals. Average baseline weight of the control group was 154.35 ± 2.39 g with the hyperglycemic animals weighing on average 148.88 ± 1.95 g (Fig. 1A). At 9 weeks after STZ injection, the average weight of hyperglycemic animals was 150.98 ± 3.11 g, while the control group weight had significantly increased to 174.38 ± 3.77 g (Fig. 1B).

Animals were injected intraperitoneally with 60 mg/kg fluorescein, and fundus images were collected using the Spectralis OCT instrument. There was no appreciable increase of fluorescence or apparent vascular deformities in the retinas of hyperglycemic rats at 4 and 9 weeks after induction of diabetes compared to control rats as seen on fluorescein angiography (Fig. 2A).

To further quantify any potential leakage, EB dye was injected into 4-week hyperglycemic animals and controls to assess leakage of albumin into the retina of these animals. Quantification of EB dye uncovered no appreciable leakage from the inner or outer BRBs in control (7.48 ± 5.4 ng/mg) and hyperglycemic (5.59 ± 2.4 ng/mg) rats. Vascular endothelial growth factor–E injected positive control eyes indicated significant leakage of albumin into the retina (37.9 ±

![Figure 1](image1.png)

**Figure 1.** Plasma glucose and weights of Brown Norway rats. Weight and plasma glucose levels were measured at baseline and 1, 4, and 9 weeks after STZ or vehicle injection. (A) While control animals gained weight throughout the experiments, hyperglycemic animals did not exhibit any significant change in weight after an initial weight loss. (B) After initial STZ injection, glucose levels quickly increased in hyperglycemic animals and remained consistently high throughout the experiment. Error bars: SEM, \( n = 11 \) to 33 rats. \( ***P < 0.001 \).

![Figure 2](image2.png)

**Figure 2.** The BRB early in diabetes. (A) Fluorescein was injected IP into diabetic and age-matched control rats at 4 and 9 weeks after STZ injection; representative images are shown. (B) Evans Blue dye (EB; 30 mg/kg), which conjugates to albumin, was injected intravenously into rats at 4 weeks. Evans Blue dye was extracted from diabetic and control neural retinas and compared to retinal weight: eyes injected with recombinant VEGF were used as positive controls. \( n = 3 \) to 4 rats. \( ****P < 0.0001 \). Error bar: 1 mm.
Error bars of bleb resorption was significantly ($P < 0.05$) reduced to 5.7 ± 0.7 l/cm²h when compared to nontreated eyes (2.43 ± 1.34 l/cm²h). As bevacizumab is a humanized antibody, dot blots were performed to determine if bevacizumab indeed binds to rat VEGF. As shown in Figure 4B, bevacizumab reacted to human and rat VEGF; however, the affinity for rat VEGF was approximately 100-fold less when compared to human VEGF. To confirm that bevacizumab can functionally block the activity of rat VEGF, the effects of rat VEGF in the presence and absence of bevacizumab (1.25 mg/mL) were evaluated in monolayer cultures of the human RPE cell line, ARPE19. Transepithelial electrical resistance measured 4 hours after rat VEGF administration was reduced by 10%, indicating cross-reactivity between rat VEGF and the human VEGF receptor system. Cells cotreated with bevacizumab (1.25 mg/mL) reversed the decreased TEER, providing further evidence that the humanized antibody has an ability to block the actions of rat VEGF (Fig. 4C).

**Disruption of RPE Tight Junctions by Hyperglycemia and VEGF**

To investigate the effects of hyperglycemia on the tight junctional integrity of the RPE, flat mounts were prepared and the localization of zona occludens-1 (ZO-1) was visualized by immunohistochemistry (Fig. 5). In hyperglycemic rats, a significant disruption of the RPE tight junctions was observed, evident in the appearance of large holes between the cells (white arrows in Fig. 5B). In age-matched sham-treated animals these holes were not present (Fig. 5A). As we have found that VEGF is at least in part responsible for the breakdown of RPE fluid transport in hyperglycemia, we also determined whether VEGF by itself can damage RPE tight junction integrity. Following intravitreal incubation with 100 ng VEGF for 24 hours, the ZO-1 staining pattern exhibited a similar appearance to that observed in hyperglycemic rats, albeit with smaller

10.9 ng/mg; Fig. 2B). Additional studies using FITC-labeled albumin in 9-week hyperglycemic animals found no albumin leakage (data not shown).

To assess if hyperglycemia resulted in retina thickening, the thickness of the retina was measured by means of segmentation in the Spectralis OCT and compared to baseline measurements for each study animal. Hyperglycemic rats exhibited an average thickness increase of 3.2 ± 2.4% at 4 weeks and 3.8 ± 0.6% at 9 weeks compared to the thickness at STZ injection. Control rats showed a lesser increase of 1.6 ± 2.0% over the original thickness at the beginning of the studies; however, there was no statistically significant difference between the hyperglycemic and control animals.

**Early RPE Dysfunction in Hyperglycemia**

To measure RPE fluid transport, we used the Spectralis OCT instrument to visualize and determine the resorption of subretinally-injected blebs in the cross section of the retina. Figure 3A displays representative blebs from a control and hyperglycemic rat. The control bleb exhibited a 50% to 60% reduction in volume by 30 minutes. However, the bleb volume was only slightly reduced at 9 weeks in the hyperglycemic rat. Quantification of the bleb volume over time (Fig. 3B) showed that by 30 minutes the volumes were reduced by 36% in controls compared to only 10% in the bleb of the hyperglycemic rats. As displayed in Figure 3C, the average rate of bleb resorption in the control animals was 7.6 ± 0.6 l/cm²h. In rats that had been hyperglycemic for 4 weeks, the average rate of bleb resorption was significantly ($P < 0.05$) reduced to 5.7 ± 0.2 l/cm²h; and following 9 weeks of hyperglycemia, the average rate was reduced further to 2.5 ± 0.7 l/cm²h ($P < 0.01$).

**VEGF Mediates RPE Dysfunction in Hyperglycemia**

To assess the involvement of VEGF in the response of the RPE to chronic hyperglycemia, we tested the ability of the anti-VEGF humanized monoclonal antibody, bevacizumab, to attenuate the dysfunction of the RPE in this rat model. Bevacizumab was administered via intravitreal injection to hyperglycemic rats 5 weeks after STZ induction of hyperglycemia, and rates were determined at 9 weeks (Fig. 4A). Eyes receiving bevacizumab showed a significant ($P < 0.05$) reduction in the rate of fluid transport (5.16 ± 1.47 l/cm²h) when compared to nontreated eyes (2.43 ± 1.34 l/cm²h).

**FIGURE 3.** Subretinal saline bleb injection. (A) Representative OCT images of subretinal blebs at 9 weeks. (B) Normalized bleb volumes after 9 weeks of hyperglycemia compared to control. (C) Rates of subretinal bleb resorption were calculated for each bleb (one per animal) by linear regression; average resorption rates for control and hyperglycemic rats are shown at 4 and 9 weeks after STZ injection and expressed as l/cm²h. Error bars: SEM, $n = 5$ to 7 rats. *$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$, ANOVA. Scale bar: 200 µm.
holes (Fig. 5D). Again, controls (saline injected rats) did not present a ZO-1 staining pattern different from normal contiguous tight junctions (Fig. 5C).

**DISCUSSION**

Research in ocular diabetes has largely focused on microvascular injury and subsequent neovascularization leading to fluid accumulation and neural retinal damage. Though it is known that the RPE is a vital component of the BRB, little work has been done directly with the RPE to uncover its contribution to the pathogenesis of ocular disorders associated with diabetes. Electron micrographs taken in the early 1980s show that the RPE microstructure changes drastically just weeks after STZ injection into rats. To corroborate these data, electroretinogram c-wave measurements show a rapidly declining RPE health in diabetic retinas. More recently, Xu et al. and Rizzolo et al. provided evidence of the breakdown of RPE tight junctions in diabetes. Other studies indicate the failing health of the neuroretina and the vascular endothelium in hyperglycemic animals; however, a more direct link between ocular diabetes, the functional deficiency of the RPE function, and DME, has not been demonstrated.

In seeking methods to answer this question, our lab first developed an in vivo rabbit model using exogenous subretinal VEGF to directly measure changes in RPE function. Subsequent studies demonstrated that intravitreal administration of glycated-albumin (an advanced glycation end-product receptor agonist) to rabbits also induces RPE dysfunction. Although these experiments showed that acute ocular exposure of the retina to VEGF and glycated-albumin can lead to a significant dysfunction of the RPE, they did not model the chronic diabetic disease state. The model used in the current study extends these previous observations into chronically hyperglycemic animals.

Although the use of diabetic rabbits would be preferential for isolating RPE function from any influence of the inner retina vasculature, the avascular rabbit retina is a model far removed from human ocular pathology. Therefore, we chose to use STZ-induced hyperglycemic rats. These rats are used regularly to study diabetes and diabetic sequelae, which benefits us with a solid basis to compare our studies to the results in the literature. In normal Brown Norway rats, rates of bleb resorption ($7.6 \pm 0.6 \mu L/cm^{2}/h$) were similar to the ones ($8.2 \pm 0.59 \mu L/cm^{2}/h$) measured previously in Dutch belted rabbits. As is shown in Figure 3, this resorptive ability of the RPE was significantly reduced as early as 4 weeks after induced hyperglycemia ($5.7 \pm 0.2 \mu L/cm^{2}/h$), and the defect became more severe as the animals aged. After 9 weeks of hyperglycemia, the average rate of bleb reabsorption was...
Reduced to 2.5 ± 0.7 μL cm⁻² h⁻¹ (P < 0.01), a reduction in the rate of resorption of over 67%.

Although microvascular changes have been reported early in diabetes²⁹,³⁰ and using STZ-induced diabetic nonpigmented Wistar rats, most studies use a longer time frame (16 weeks) to study this disease, particularly in pigmented rats, which seem to be somewhat protected from early ocular symptoms.³⁰ In our hands, no apparent leakage, retinal thickening, or obvious vascular deformities were observed via four independent modalities in the hyperglycemic animals (Fig. 2).³⁰ Neither in vivo angiography with fluorescein, nor EB assays exhibited appreciable leakage into the retinal space, though other groups have reported leakage measured by EB in diabetic rats soon after STZ injection.³¹ As there were no appreciable vascular abnormalities at the time points investigated in this study, nor was there any significant increase in retinal thickness, we concluded that the reduced rates of RPE fluid reabsorption in our hyperglycemic rats still were sufficient to maintain fluid balance in the neuroretina. Unfortunately, the development of diabetic cataracts after 10 weeks of hyperglycemia has had a role in that process. Certainly, VEGF can induce RPE endothelial growth factor, which is present in the serum, may have a role via PKC/β downstream of an initial activation of RAGE.⁴⁻²⁸ Thus, dysfunctional tight junctions appear to be the reason for the breakdown of RPE fluid transport. Similar observations were presented previously by Le et al.,¹⁴,¹⁵ showing RPE barrier breakdown in diabetes.

In conclusion, from these results and previous work performed in our laboratory,¹¹,¹²,¹⁹ we hypothesize that the loss of RPE function has a vital role in the deterioration of the retina early in hyperglycemia. Streptozotocin-induced, hyperglycemic rats pose difficulties for studying retinal edema because they: (1) do not have a macular region and (2) do not have edema as a result of hyperglycemia before diabetic cataracts become established. The experiments described in the current study do not represent a direct model of human edema. However, they do indicate that fundamental properties of the RPE responsible for fluid homeostasis are significantly impaired by even a few weeks of hyperglycemia. Thus, the role of the RPE in the development of DME should not be overlooked when addressing the pathogenesis of this disease.

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RPE Breakdown in Hyperglycemia

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