Retinal Ischemia and Reperfusion Causes Capillary Degeneration: Similarities to Diabetes

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PURPOSE. Retinal neurons and vasculature interact with each other under normal conditions, and occlusion of the retinal vasculature can result in damage to retinal neurons. Whether damage to the neural retina will damage the vasculature, however, is less clear. This study was conducted to explore the relationship between vascular and nonvascular cells of the retina. The response of the retinal vasculature to an injury (ischemia and reperfusion; I/R) that is known to cause neuronal degeneration was studied.

METHODS. I/R injury to the retinas was induced in Lewis rats and C57BL/6j mice by elevating intraocular pressure (IOP), and reperfusion was established immediately afterward. Some rats were pretreated with aminoguanidine (AMG, 50 mg/Kg BW in drinking water) before the procedure. Poly(ADP-ribose) polymerase (PARP) activity and expression of inducible nitric oxide synthase (iNOS), and cycloxygenase-2 (COX-2) were measured by Western blot analysis, and levels of TNF-α and intercellular adhesion molecule (ICAM)-1 mRNA were measured by qPCR at 2 and 7 days after the procedure. Also at 2 and 7 days after the I/R injury, apoptosis of retinal neural cells (demonstrated by TUNEL assay), density of cells in the ganglion cell layer, and the number of degenerated capillaries were quantitated, and the number of TUNEL-positive capillary cells and degenerated capillaries were assessed. Retinal neurodegeneration and capillary degeneration were also examined in C57BL/6j mice 2, 5, 8, and 14 days after I/R injury.

RESULTS. As expected, loss of cells in the retinal ganglion cell layer was apparent 2 days after I/R injury in the rat and mouse models. In contrast, the retinal vasculature had essentially no pathology at this time in either model. Surprisingly, the number of degenerated capillaries increased greatly by 7 to 8 days after the injury. Administration of aminoguanidine significantly inhibited I/R-induced capillary degeneration as well as neurodegeneration in the rat model. Retinal I/R caused increased PARP activity (detected by poly(ADP-ribose)lated proteins), as well as upregulation of iNOS, COX-2, TNF-α, and ICAM-1 levels in rats, consistent with an inflammatory process.

CONCLUSIONS. Capillary degeneration is an unrecognized component of acutely elevated IOP and develops only after neurodegeneration is severe. Thus, this finding raises the possibility that damage to the neural retina contributes to capillary degeneration. Aminoguanidine, a nonspecific inhibitor of iNOS, inhibited I/R-induced degeneration of both neuronal and vascular cells of the retina. The model of retinal ischemia and reperfusion will be a useful tool for investigating the relationship between neuronal damage and vascular damage in glaucoma and other diseases such as diabetic retinopathy. (Invest Ophthalmol Vis Sci. 2007;48:361–367) DOI:10.1167/iovs.06-0510

During embryogenesis, the development and differentiation of the retina requires the concomitant formation of neuronal and glial elements, along with a dense vascular network.1 In adults, all these three compartments interact with each other to maintain normal retinal structure and function.1 Damage to the function of the retinal vasculature is known to damage the neuroglial retina in branch vein occlusion, and conversely, it seems reasonable that alterations in the neuroglial retina may affect the vasculature.2 In diabetes, dysmetabolism or apoptosis of cells in the neuroglial retina has been postulated to contribute to degeneration of retinal capillaries.3 Retinal ischemia contributes to visual impairment and blindness in diseases such as acute closed-angle glaucoma4 and diabetic retinopathy.5 One of the most frequently used models for the investigation of molecular mechanisms and potential therapeutic strategies for retinal ischemia has been a rat model of acute elevation of intraocular pressure (IOP) followed by reperfusion (I/R). Histologic studies demonstrate that there is serious perturbation of neuronal and glial elements of the retina during the ischemia and reperfusion injury, whereas there has been no investigation of the vasculature of this model thus far.

Several laboratories have demonstrated that nitric oxide neurotoxicity is responsible, at least in part, for the neuronal degeneration after retinal I/R injury.6,7 Aminoguanidine has been reported to protect retinal neurons in retinal I/R injury and glaucoma due to its potent ability to inhibit inducible nitric oxide synthase (iNOS).7–9 Most investigations have found that iNOS is upregulated in glial cells of the retina in I/R.6,7 We have begun to investigate this I/R model as an approach to understanding the potential role of the nonvascular retina in the degeneration of retinal capillaries. Our studies demonstrate that capillary degeneration occurs in the retinal I/R model and that it develops only after severe neurodegeneration has occurred. In addition, the neuroprotective effects of aminoguanidine also result in protection of the retinal vasculature.

MATERIALS AND METHODS

Rat Model of Retinal Ischemia-Reperfusion

Male Lewis rats weighing 200 to 250 g and male C57BL/6j mice weighing 25 to 30 g were anesthetized. The anterior chamber of one eye was cannulated with a 30-gauge needle attached to a line infusing normal saline. IOP was measured by a handheld tonometer (TONO Pen; Medtronic Solan, Jacksonville, FL) in rat eyes, and pressure in the...
eye was regulated to 80 to 90 mm Hg with a pressure infuser (Infu-surg; Ethox Corp., Buffalo, NY). The other eye of the same animal was set up as a control. The same pressure was also applied to the mouse model. The duration of ischemia was 120 minutes for rats and 90 minutes for mice. After ischemia, the needle was withdrawn, IOP was normalized, and reflow of the retinal circulation was documented visually. Some rats were pretreated with aminoguanidine (AMG, 50 mg/kg body weight in drinking water) 2 days before the procedure. Animals were killed at different times after I/R injury. All procedures involving the animals conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

**Ganglion Cell Count and Retinal Thickness in Sections of Whole Retina**

The enucleated eyes were routinely fixed in 10% buffered formalin, embedded in paraaffin and stained with periodic acid-Schiff and hematoxylin (PASH) for light microscopy and morphometry of retinal thickness. The nuclei in the ganglion cell layer (not including nuclei in the vessels) were counted, and the thickness of retinal layers was measured in four locations in the retina (both sides of the optic nerve [posterior] and mid retina [central]) for rats and six locations in the retina for mice under 400× with an ocular micrometer. The thickness of retinal layers was measured as follows: the first layer was the combined ganglion cell layer and inner plexiform layer (GCL+IPL), the second layer included the inner nuclear layer and the outer plexiform layer (INL+OPL), and the third layer consisted of the outer nuclear layer (ONL).

**Quantitative PCR (qPCR)**

Total RNA was isolated from the retinas (TRizol LS reagent; Invitrogen, Gaithersburg, MD). The concentration of RNA was measured by a spectrophotometer (DU-600; Beckman Instruments, Fullerton, CA) at 260 nm. qPCR was performed as previously described. Briefly, reverse transcription was performed with 1 μg of total RNA using the superscript first-strand synthesis system (Invitrogen, Gaithersburg, MD). qPCR used a PCR core reagent (SYBR green; Applied Biosystems, Inc. [ABI], Foster City, CA) in a 24-μL volume, with a sequence detection system (Prism 7000; ABI). Transcript-specific primers were designed using primer express software (ABI), and their specificities were confirmed by the use of NCBI Blast. β-Actin was used as the internal control. The sequences for TNF-α, ICAM-1, and β-actin were as follows: TNF-α: upstream primer, 5'-GACAGGCGCTGGCAGGACTA-3'; downstream primer, 5'-AGGCCCTCTTGGACAGAGA-3'; ICAM-1: upstream primer, 5'-TCACTCGTGAAATATGCGT-3'; downstream primer, 5'-AGGGCCCTTCATTGTTGCAA-3'; and β-actin: upstream primer, 5'-AGGCCAACCGTGAAGATG-3'; downstream primer, 5'-ACCAGAGGCTACAGGCA-3'. Each sample was tested in triplicate. The relative difference was expressed as the 2^{-ΔΔCT} method. Agarose gel electrophoresis was used to confirm that reaction products had the expected size. The formation of a single product was also confirmed by observing the melting curve graph that was generated by the sequence-detection system for each reaction tube.

**Western Blot Analysis**

Rat retinas were isolated and sonicated in RIPA buffer (Santa Cruz Biotechnology, Santa Cruz, CA). The total amount of protein was determined by protein assay (Bio-Rad, Hercules, CA). Samples (20–50 μg protein) were separated by SDS-PAGE and electroblotted to nitrocellulose membrane, and the membranes were blocked in Tris-buff ered saline, 0.02% Tween 20, containing 5% nonfat milk. Antibodies for poly(ADP-ribose) groups (1:2000 dilution; Alexix Biochemicals, San Diego, CA), iNOS (1:1000 dilution; Sigma-Aldrich, St. Louis, MO), and COX-2 (1:1000 dilution; Cayman Chemical, Ann Arbor, MI) were applied overnight at 4°C. All blots were washed and incubated with horseradish peroxidase-coupled secondary antibody at a dilution of 1:3000. After extensive washing, protein bands detected by the anti-bodies were visualized by ECL reagent (Santa Cruz Biotechnology) after exposure on autoradiograph film (X-OMAT; Eastman Kodak Scientific Imaging Film, New Haven, CT). Membranes then were stripped and re-probed with β-actin (Sigma-Aldrich) to confirm equal protein loading. The films were subsequently scanned, and band intensities were quantified (Quantity One 1-D Analysis Software; BioRad). The protein expression levels were then quantitated relative to β-actin in the same sample and normalized to control retinas.

**Isolation of Retinal Vasculature**

Retinal vasculatures were isolated as described by us previously. Briefly, freshly isolated eyes were fixed with 10% neutral buffered formalin for 1 day. Retinas were isolated, washed in water overnight, and then incubated with 3% crude trypsin (Difco; BD Biosciences, Sparks, MD) at 37°C for 1 hour. Nonvascular cells were gently brushed away from the vasculature, and the isolated vasculature laid out on slides and used for TUNEL assay and acellular capillary examination.

**TUNEL Assay**

At 2 or 7 days after the onset of ischemia, the TUNEL reaction (In Situ Cell Death Detection kit, fluorescein; Roche, Mannheim, Germany) was performed to detect retinal cell death on the isolated vasculature and on retinal cross sections. In each assay, a positive control was set up by treatment with DNase (50 U/100 μL) for 10 minutes, to fragment DNA on an additional slide.

**Retinal Blood Vessels**

The retinal vasculature (isolated by the trypsin digest method) was washed extensively in PBS and then permeabilized with 1% Triton X-100 in PBS. The TUNEL reaction was performed in a humidified atmosphere at 37°C for 1 hour. The number of TUNEL-positive nuclei in different groups was counted in the entire retinal vasculature.

**Paraffin-Embedded Retinal Sections**

Paraffin-embedded sections (5 μm) were deparaffinized in xylene and rehydrated in decreasing concentrations of ethanol. High-temperature antigen retrieval was performed in an antigen-unmasking solution (Vector Laboratories, Burlingame, CA) for 20 minutes, and the TUNEL reaction was performed as just described.

**Quantitation of Degenerated (Acellular) Capillaries**

After quantitation of TUNEL-positive cells, the coverslips were gently soaked away from the slides. Sections were then stained with PASH. Acellular capillaries were quantitated as we have reported for diabetic retinopathy (200× magnification for rat retinas and 400× magnification for mouse retinas). Acellular capillaries were identified as capillary-sized vessel tubes having no nuclei anywhere along their length and are reported per square millimeter of retinal area.

**Statistical Analysis**

All results were expressed as the mean ± SD. Most data were analyzed by the nonparametric Kruskal-Wallis test followed by the Mann-Whitney test, except the results of qPCR and TUNEL assay on retinal sections. Those tests were analyzed by t-test and nonparametric sign test, respectively. Differences were considered statistically significant at P < 0.05.

**RESULTS**

**Effect of I/R on Neurons in Rat Retinas**

I/R-induced retinal damage was assessed histologically 2 and 7 days after the injury (Fig. 1, Table 1). Two days after I/R, 77% of cells in the GCL in the posterior regions of the retina and 62% of cells in GCL in the central regions of the retina had been lost. Seven days after ischemia, there was no further loss of cells in the posterior region, whereas there was a 79% loss in
Effect of I/R on Retinal Capillaries in Rats

Examination of retinal vasculature 2 days after the I/R injury (Fig. 2). Two days after I/R injury, there was a significant increase in TUNEL-positive cells in the GCL, INL, and ONL (especially in INL; \( P < 0.05 \), Fig. 2B), whereas no TUNEL-positive cells were observed in control eyes (Fig. 2A). At 7 days after I/R injury, there were still some TUNEL-positive cells, although fewer than 2 days after the injury (Fig. 2C).

Effect of I/R on Retinal Capillaries in Rats

Examination of retinal vasculature 2 days after the I/R injury (a time when there was extensive degeneration of neuronal retina) showed a significant but slight increase in the number of TUNEL-positive capillary cells in the injured retinas compared with the control retinas obtained from the same animal (24.7 ± 9.9 vs. 9.3 ± 4.0 TUNEL-positive cells per retina; \( n = 3 \) of each group; \( P < 0.05 \)).

Increased death of retinal capillary cells leads to degeneration of entire capillaries in other ocular diseases, such as diabetic retinopathy. We investigated whether the death of retinal capillary cells in the I/R model likewise resulted in degeneration in the retinal capillaries. Two days after the I/R injury, there was no significant increase in the number of acellular capillaries in the injured retinas compared with the control retinas of the same animal (3.6 ± 0.8 vs. 3.5 ± 0.9 acellular capillaries per mm² retina; \( n = 3 \) of each group; Fig. 4B). Seven days after the injury, however, there was a dramatic increase in the number of degenerated, acellular capillaries in the injured retina compared with the control retinas (23.5 ± 0.8 vs. 4.5 ± 0.5 acellular capillaries/mm² retina; \( n = 5 \) of each group; \( P < 0.01 \); Fig. 4B).

Effect of Aminoguanidine on I/R-induced Degeneration of Retinal Vascular Cells and Neuronal Cells in Rats

Aminoguanidine has been reported to have a neuroprotective effect in the retina. Consistent with those reports, aminoguanidine treatment (assessed 7 days after I/R) resulted in significant protection against cell loss in the ganglion cell layer.

### Table 1. Aminoguanidine Inhibited the Changes of Retinal Thickness Caused by Ischemia and Reperfusion

<table>
<thead>
<tr>
<th>Group</th>
<th>Posterior Retina</th>
<th>Central Retina</th>
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<tbody>
<tr>
<td></td>
<td>GCL + IPL (( \mu m ))</td>
<td>INL + OPL (( \mu m ))</td>
</tr>
<tr>
<td>2 Days after I/R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (( n = 5 ))</td>
<td>71.6 ± 3.0</td>
<td>41.7 ± 1.8</td>
</tr>
<tr>
<td>I/R (( n = 5 ))</td>
<td>42.7 ± 9.2*</td>
<td>28.4 ± 1.9*</td>
</tr>
<tr>
<td>7 Days after I/R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (( n = 5 ))</td>
<td>77.5 ± 10.8</td>
<td>43.6 ± 2.3</td>
</tr>
<tr>
<td>I/R (( n = 5 ))</td>
<td>14.8 ± 9.5*</td>
<td>18.7 ± 10.1*</td>
</tr>
<tr>
<td>I/R pretreated with AMG (( n = 6 ))</td>
<td>42.9 ± 24.4</td>
<td>31.8 ± 8.9†</td>
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* \( P < 0.05 \) compared to control retinas.
† \( P < 0.05 \) compared to I/R injured retinas.
the regulation of TNF-α and ICAM-1 mRNA after I/R injury in the retina, we isolated total RNA from the experimental retinas 2 and 7 days after I/R injury and from the control retinas. There was a significant increase of TNF-α and ICAM-1 levels in the retinas 2 and 7 days after injury compared with the control retinas (Table 2; \( n = 3 \) per time point; \( P < 0.05 \)). Significant increases in TNF-α and ICAM-1 mRNA were also confirmed by using 18s rRNA as the internal control (data not shown).

Other inflammatory markers, including COX-2, iNOS, and activity of poly(ADP-ribose) polymerase (PAR), were measured by Western blot analysis 2 or 7 days after retinal I/R injury (Fig. 5A). Two days after I/R injury, there were 6.3-, 2.7-, and 2.0-fold increases in COX-2, iNOS, and PAR expression levels, respectively, in the injured retinas (\( n = 3 \)) compared with the control retinas (\( n = 5 \); \( P < 0.05 \); Fig. 5B). Seven days after the injury, COX-2 expression remained 4.4-fold greater than the normal level (\( P < 0.05 \); Fig. 5C), but there were no longer significant differences in iNOS and PAR expression levels between injured retinas (\( n = 3 \)) and control retinas (\( n = 4 \)). Upregulation of these inflammatory markers were found to precede vascular damage in the retinal I/R injury.

**Neurodegeneration and Vascular Degeneration in Mouse Retina**

To investigate whether retinal I/R injury causes vascular degeneration also in other species, we induced I/R injury in mice (C57BL/6J). As demonstrated in Figure 6A, 40% of cells in GCL of the mouse retina had been lost 2 days after I/R. Five days after the injury, there was an approximately 70% loss of cells in the GCL, and there was no further loss of cells after longer durations. Likewise, consistent with the rat model, capillary degeneration was not apparent until after the neurodegenerative phase. There was no capillary degeneration apparent 2 and 5 days after I/R injury (\( n = 4 \) of each group). Eight days after the injury, however, there was a significant increase in the number of degenerated, acellular capillaries in the injured retina compared with the control retinas (\( n = 5 \) of each group), and the number of degenerated capillaries was continuing to increase 14 days after I/R injury (\( n = 4 \) of each group; Fig. 6B).

**Figure 3.** Administration of aminoguanidine inhibited capillary cell death after retinal I/R in rats. (A) An example of TUNEL-positive capillary cells (red arrows) in the retinal vasculatures of injured retinas at 7 days after I/R by trypsin-digested method (top), PASH staining of the same area (bottom) showed condensed or fragment nuclei of TUNEL-positive cells (red arrows). (B) Inhibition of retinal I/R-induced capillary cell death by pretreatment with aminoguanidine. (\( n = 3–5 \) in each group; \( * P < 0.05 \) compared to control retinas; \( ** P < 0.05 \) compared to I/R-injured retinas).

**Figure 4.** Administration of aminoguanidine inhibited capillary degeneration after retinal I/R in rats. (A) Examples of degenerated, acellular capillaries (black arrows) in the retinal vasculature of I/R-injured retina (right) and control retina (left). (B) Inhibition of capillary degeneration in injured retinas by pretreatment with aminoguanidine. (\( n = 3–5 \) in each group; \( * P < 0.05 \) compared to control retinas; \( ** P < 0.05 \) compared with I/R-injured retinas).
Capillary Degeneration in Ischemia-Reperfusion

**Figure 5.** Retinal I/R caused up-regulation of several inflammatory markers in rats. (A) Western blots of retinal COX-2, iNOS and activity of PARP (estimated by detection of poly(ADP-ribosyl)ated proteins) 2 and 7 days after retinal I/R. (B) Quantitative data of expressions of different inflammatory markers 2 days after retinal I/R. *P < 0.05 compared with control retinas (control, n = 5; I/R injury, n = 5). (C) Quantitative data of expressions of different inflammatory markers 7 days after retinal I/R. *P < 0.05 compared to control retinas (control, n = 4; I/R injury, n = 5).

**Table 2.** Time Course for Expression of ICAM-1 and TNF-α mRNAs after Retinal I/R Injury: qPCR Results

<table>
<thead>
<tr>
<th>ICAM-1</th>
<th>C&lt;sub&gt;T&lt;/sub&gt; of ICAM-1</th>
<th>C&lt;sub&gt;T&lt;/sub&gt; of β-Actin</th>
<th>ΔΔC&lt;sub&gt;T&lt;/sub&gt;</th>
<th>Change (x-Fold)</th>
</tr>
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<tr>
<td>2 days after injury</td>
<td>I/R injured</td>
<td>24.9 ± 0.4</td>
<td>22.2 ± 0.2</td>
<td>-1.27</td>
</tr>
<tr>
<td>control</td>
<td>25.9 ± 0.8</td>
<td>21.9 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 days after injury</td>
<td>I/R injured</td>
<td>24.5 ± 0.3</td>
<td>23.5 ± 1.1</td>
<td>-1.71</td>
</tr>
<tr>
<td>control</td>
<td>25.4 ± 0.4</td>
<td>22.8 ± 0.4</td>
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<table>
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<tr>
<th>TNF-α</th>
<th>C&lt;sub&gt;T&lt;/sub&gt; of TNF-α</th>
<th>C&lt;sub&gt;T&lt;/sub&gt; of Actin</th>
<th>ΔΔC&lt;sub&gt;T&lt;/sub&gt;</th>
<th>Change (x-Fold)</th>
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<tbody>
<tr>
<td>2 days after injury</td>
<td>I/R injured</td>
<td>25.0 ± 0.3</td>
<td>22.2 ± 0.2</td>
<td>-1.13</td>
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<tr>
<td>control</td>
<td>25.9 ± 0.9</td>
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<tr>
<td>7 days after injury</td>
<td>I/R injured</td>
<td>24.5 ± 0.1</td>
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<tr>
<td>control</td>
<td>25.5 ± 0.3</td>
<td>22.8 ± 0.4</td>
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n = 3 per time point. The extensive cell death (see Figure 2) at 7 days after I/R injury may account for seemingly decreased β-actin mRNA levels (although statistical significance was not achieved) in I/R-injured retinas compared with control retinas.

*P < 0.05 compared to control retinas.

**DISCUSSION**

In the present study, we demonstrated that retinal I/R causes capillary degeneration as well as the expected neuronal degeneration. Moreover, based on the time-course of degeneration of both the neuronal and vascular compartments, significant neuronal loss in the retina precedes capillary degeneration. iNOS apparently contributes to the degeneration of both the neural and vascular compartments, since aminoguanidine, a known (but nonspecific) inhibitor of iNOS, inhibited degeneration in both compartments.

There are at least four possibilities for the cause of the capillary degeneration seen in this model. First, the release of toxic factors or loss of trophic factors from the damaged neuroglial cells of the retina may result in capillary degeneration. Second, activated leukocytes or other inflammatory cells such as infiltrated macrophages may stimulate cell death signaling in capillary cells, leading to capillary degeneration. Consistent with this, the inflammatory response after retinal I/R involves the activation and infiltration of peripheral leukocytes from the retinal circulation into the retina. Third, capillary degeneration may be due to failure of endothelial hematopoietic stem cells to maintain normal retinal vasculature or to repair damaged vasculature. Endothelial precursor cells can re-endothelialize acellular capillaries after I/R injury (Caballer<sub>o</sub> Jr et al. IOVS 2006;47:ARVO E-Abstract 3525) and can rescue and stabilize degenerating vasculature in rd1/rd1 mice. Finally, direct damage to the vasculature as result of thrombosis, pressure-induced damage, or reactive oxygen species all could contribute to capillary degeneration in this I/R model.

In this study, we investigated several inflammatory markers including ICAM-1 and TNF-α at transcriptional level, as well as PARP activity, iNOS and COX-2 at expression level (Fig. 5, Table 2). All these molecules, possibly released by activated inflammatory cells, glial elements, and injured neurons, are consistent with an acute inflammatory process in the retinal I/R model. Recent evidence that these proinflammatory proteins play a major role in degeneration of retinal capillaries in diabetes (Zheng L, et al. IOVS 2006;47:ARVO E-Abstract 1712) raise a possibility that I/R-induced release of proinflammatory molecules contributed to the observed capillary degeneration in the I/R model as well.
Morphologically, degenerated capillaries in retinal I/R seem comparable to acellular capillaries found in diabetic retinopathy. Degenerated, acellular capillaries are not perfused, and are believed to represent a discrete event that progressively contributes to the development of retinal ischemia, and ultimately, to neovascularization.\textsuperscript{19,20} Of note, several therapies reported to inhibit retinal neurodegeneration after I/R\textsuperscript{7,9,21–23} also have been reported to have beneficial effects against the development of early microvascular lesions of diabetic retinopathy.\textsuperscript{15,24–27} Retinas from rodents after I/R show biochemical alterations that also are seen in diabetes, including increased expression of iNOS\textsuperscript{28} and ICAM-1\textsuperscript{29–33} and activation of caspase-1.\textsuperscript{34–35} Based on this similarity between I/R and diabetic retinopathy, we postulate that the retinal I/R model may be used as an acute model for screening therapeutic approaches to inhibit capillary degeneration in diabetic retinopathy and other retinopathies.

The relationship between the loss of capillaries and nonvascular cells in the retina has remained largely unexplored. The I/R model may prove useful in investigations of this relationship. Evidence that neuroglial degeneration precedes the degeneration of retinal capillaries in this model is consistent with the possibility that damage to the neuroglial retina causes or contributes to the capillary degeneration. This notion should be further explored in the I/R model and in diabetic retinopathy. The rapid development of retinal vascular degeneration like that common in diabetes may make this model suitable for high-throughput testing of pharmacological approaches to inhibit diabetic retinopathy.

References


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