Effect of Acute Hyperglycemia on Oxygen and Oxidative Metabolism in the Intact Cat Retina

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PURPOSE. The Crabtree effect is the phenomenon of inhibition of respiration by glycolysis, as a result of elevated glucose levels. It is not certain whether the Crabtree effect occurs in the retina, which has a high glycolytic capacity. In the current study, in vivo photoreceptor oxygen consumption was examined during the normo- and hyperglycemic states in the dark-adapted cat retina to determine whether the Crabtree effect occurs in the outer retina.

METHODS. Spatial profiles of oxygen tension were obtained in the cat retina, in vivo, with the use of oxygen microelectrodes during control conditions and acute (5.19 ± 0.83 hour) episodes of hyperglycemia (blood glucose, >350 mg/dL). The outer retinal portions of the profiles were fitted to a model of oxygen diffusion to quantify photoreceptor oxygen consumption.

RESULTS. Photoreceptor oxygen consumption did not significantly change during hyperglycemia compared with control conditions. Choroidal PO2 decreased during hyperglycemia by an average of 5.8 ± 7.4 mm Hg. This led to an increase in the fraction of O2 used by the photoreceptors that was derived from the inner retina. Choroidal PO2 did not recover when blood glucose levels were returned to normal. Average inner retinal PO2 was not affected by the episodes of hyperglycemia.

CONCLUSIONS. The Crabtree effect does not occur to any significant degree in the outer retina, because hyperglycemia did not affect photoreceptor oxygen consumption. Choroidal PO2 decreased during hyperglycemia, and the oxygen deficit was made up by the retinal circulation. (Invest Ophthlalmol Vis Sci. 2003;44:745–750) DOI:10.1167/iovs.02-0452

The Crabtree effect is the inhibition of respiration by glycolysis caused by elevated glucose levels. It occurs when adenosine diphosphate (ADP) and inorganic phosphate (Pi), both needed for glucose oxidation (respiration), remain at very low concentrations because of a high rate of glycolysis, leaving little ADP for production of oxidative adenosine triphosphate (ATP). It is not certain whether the Crabtree effect occurs in the retina, which has an extremely high glycolytic capacity.1–5 Wang et al.5,6 have shown that the outer retina (photoreceptor layer) is where most of the retinal glycolysis takes place in feline and porcine retinas. In the intact porcine retina, more than 80% of the glucose extracted from the choroid is converted to lactate; whereas only 20% of the glucose extracted from the retinal circulation is converted to lactate.6

Cohen and Noell7 did not observe a Crabtree effect in rabbit photoreceptors. They found the effect in the inner retina of adult rabbits and in young rabbits before the photoreceptors were fully developed, but this may not be relevant to the more highly vascularized feline or human inner retina. In support of the independence of outer retinal oxidative and glycolytic metabolism, an enzyme-localization study showed that lactate dehydrogenase (LDH), the enzyme that converts pyruvate to lactate, is present primarily in areas without mitochondria in the photoreceptor in the monkey retina.8

In contrast, Van den Enden et al.9 showed a 31% increase in lactate production in the isolated rat retina when the glucose concentration in the bath solution was increased from 5 to 20 mM. An increase in lactate production of 25% was confirmed by Winkler et al.10 when the experiments were repeated. However, they also observed a greater tissue ATP content in the retina bathed in the high-glucose medium.10 Because the ATP content in 20 mM glucose was the same as that observed in the intact rat retina, they concluded that 5 mM did not provide the isolated retina with enough glucose to support normal metabolism. They suggested that more glucose is needed in vitro, because there is an increased diffusional resistance, probably resulting from the presence of unstirred layers adjacent to the tissue and a nonperfused retinal circulation. Thus, the increased glycolysis was not considered evidence of a Crabtree effect.

In long-term hyperglycemia (diabetes), indirect evidence has been obtained in support of a retinal Crabtree effect. Rimmer and Linsenmeier11 found that the RPE c-wave was more resistant to hypoxia in diabetic rats than in healthy control animals. One interpretation of this finding was that the diabetic rats have an increased reliance on glycolysis. Linsenmeier et al.12 have also observed a decrease in outer retinal O2 consumption (QO2) in long-term diabetes in cats. However, this decrease in QO2 most likely resulted from the decreased choroidal PO2 that was observed in the study, rather than the Crabtree effect. QO2 is positively correlated with choroidal PO2.13,14 It is also possible, but less likely, that an adaptive mechanism in the choroid, as a consequence of a decreased O2 demand, lowered choroidal PO2.

In the current set of experiments, we directly examined outer retinal oxidative metabolism during normoglycemia and acute hyperglycemia to determine whether the Crabtree effect occurs in the intact cat retina. In addition, measurements during hyperglycemia may give insight into processes occurring during diabetes. The outer (distal) portion of the intraretinal O2 tension (PO2) profile was fitted to a diffusion model to quantify photoreceptor O2 consumption. Profile parameters were also used to examine other aspects of oxidative metabolism in the outer retina. The inner retinal portion of PO2 profiles allowed the examination of inner retinal oxygenation and O2 autoregulation during hyperglycemia.

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Supported by Grants R01-EY05034 and T32-EY07128 from the National Eye Institute.

Submitted for publication May 1, 2002; revised July 8, 2002; accepted July 16, 2002.

Commercial relationships policy: N.

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METHODS

Animal Preparation

All efforts were made to minimize the pain and discomfort of the animals, and all procedures adhered to the guidelines of the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Nine adult male cats were initially anesthetized by either an intramuscular injection of ketamine (25 mg/kg) and acepromazine (3 mg) or an intravenous infusion of 5% pentothal sodium (22 mg/kg). Five percent pentothal was then administered as needed for the remainder of surgical preparations. Urethane was also administered at 400 mg/h during surgery until a loading dose of 200 to 400 mg/kg was reached.

Two saphenous veins and one femoral artery were cannulated for drug delivery and blood pressure monitoring, respectively. A tracheotomy was also performed to allow artificial respiration after induction of paralysis when all surgical procedures were completed.

The cat was placed on its back in a Faraday cage. The head was secured in a head holder with the eyes facing upward. An incision, approximately 5 in. long, was made from the lateral canthus toward the ear. The underlying fascia and muscle were resected to cleanly expose the cartilage and bone of the orbit. The nictitating membrane was clamped and removed. Enough bone and cartilage were dissected to accommodate the electrode manipulator. The fascia and muscle on the orbit itself were resected, and the eye was hung on an eye ring by the conjunctiva for stabilization. The animal was paralyzed by an intravenous infusion of pancuronium bromide (2 mg). Both pancuronium bromide–induced paralysis and anesthesia with urethane were continued for the remainder of the experiment, with maintenance doses of 0.2 mg/kg per hour and approximately 25 mg/kg per hour, respectively. The animal was artificially ventilated at a rate and volume suitable for maintaining arterial blood gas levels within the normal limits (i.e., PaO$_2$ ≈ 90 mm Hg, PaCO$_2$ ≈ 30–40 mm Hg, 7.35 < pH < 7.45). Blood gas levels, glucose, and lactate were measured with a blood gas analyzer (model 860; Bayer/Ciba-Corning, Norwood, MA). A 15-gauge needle was then placed through the sclera into the vitreous humor. A calibrated oxygen-voltage microelectrode was placed through the needle lumen and attached to a hydraulic micropipette (David Kopf, Tujunga, CA) to allow micrometer control of the electrode position. A Silastic (T-2; Dow Corning, Midland, MI) boot was used to accommodate the electrode manipulator. The fascia and muscle on the ear were resected to cleanly expose the cartilage and bone of the orbit. The nictitating membrane was clamped and removed. Enough bone and cartilage were dissected to accommodate the electrode manipulator. The fascia and muscle on the orbit itself were resected, and the eye was hung on an eye ring by the conjunctiva for stabilization. The animal was paralyzed by an intravenous infusion of pancuronium bromide (2 mg). Both pancuronium bromide–induced paralysis and anesthesia with urethane were continued for the remainder of the experiment, with maintenance doses of 0.2 mg/kg per hour and approximately 25 mg/kg per hour, respectively. The animal was artificially ventilated at a rate and volume suitable for maintaining arterial blood gas levels within the normal limits (i.e., PaO$_2$ ≈ 90 mm Hg, PaCO$_2$ ≈ 30–40 mm Hg, 7.35 < pH < 7.45). Blood gas levels, glucose, and lactate were measured with a blood gas analyzer (model 860; Bayer/Ciba-Corning, Norwood, MA).

Oxygen-Voltage Microelectrode

Recasted, polarographic double-barreled oxygen electrodes were used. The oxygen-sensing barrel consisted of a gold cathode, polarized to a constant voltage (−0.7 V) in comparison with an Ag/AgCl reference. The electrode was calibrated immediately before use in a saline-filled tonometer bubbled with gases at a known PO$_2$. Three calibration points were taken at 0%, 4%, and 8% O$_2$ (PO$_2$ = 0, 28, and 56 mm Hg, respectively). The electrodes produced a current on the order of a few femtoamperes, which was linear in its relation to the PO$_2$ at the electrode’s tip. The current was measured by a picocoumeter (614 Electrode; Keithley Instruments, Cleveland, OH) which converted the current to a voltage. The second barrel, filled with 0.9% NaCl, acted as a voltage electrode to record local intraretinal ERGs. Overall electrode tip diameters ranged from 5.0 to 6.5 μm with cathode diameters ranging from 1 to 2 μm. The sensitivity of the electrodes was on the order of 10$^{-15}$ to 10$^{-14}$ A/mm Hg.

Stimuli

ERGs were recorded in response to a 4-second flash of diffuse white light. Light stimuli were produced by a tungsten iodide H1 automobile headlamp bulb, which had a maximum illumination of 9.4 (equivalent log quanta [555 nm] per degree squared per second). The light source was contained in an optical bench located outside the Faraday cage and was brought to the cat through a fiber-optic bundle. A neutral-density wedge filter was used to attenuate the light source. A timer (A-65 Timer/Stimulator; Winston Electronics Co., San Francisco, CA) controlled the light shutter (ST-2 shutter driver; Winston Electronics Co., San Francisco, CA; Uniblitz shutter; Vincent Associates, Rochester, NY).

Data Collection

The oxygen current was recorded from the oxygen barrel, whereas local ERGs, referenced to a scalp Ag/AgCl electrode, were collected from the voltage barrel. The retina was penetrated by advancing the microelectrode in 3-μm steps. Local ERGs were recorded every 30 μm to assess the position of the electrode in the retina. On reaching the choroidal circulation, as indicated by high oxygen levels and the transepithelial potential across the RPE, the electrode was withdrawn at a steady 2 μm/sec while continuously recording the oxygen current, generating a profile of PO$_2$ as a function of position. For analysis of the profiles, the position of the RPE was taken to be the point at which PO$_2$ began to decrease, and the position of the vitreal border was taken to be the point at which the ERG recorded with the microelectrode and the ERG recorded with the vitreal electrode were the same. Several normoglycemic profiles (blood glucose, 80–120 mg/dL) were recorded under dark-adapted conditions. The cat was then made hyperglycemic (blood glucose >350 mg/dL) through continuous intravenous infusion of 40% glucose. Whenever possible, blood glucose was returned to the normal range with continuous intravenous infusion of insulin, and recovery profiles were collected. Recovery from hyperglycemia was achieved in five of the nine cats.

Modeling of Outer Retinal Oxygen Tension

A three-layer diffusion model, developed and fully described by Haugh et al. and Braun et al., was fitted to the outer half of intraretinal PO$_2$ profiles, corresponding to the avascular portion of the retina. Briefly, the outer retina was divided into three anatomic layers: the RPE and photoreceptor outer segments (OS), the photoreceptor inner segments (IS), and the outer nuclear layer and outer plexiform layer (ONL-OPL). Because mitochondria are localized to the photoreceptor IS, oxygen consumption is nonzero only in the IS layer (Fig. 1). The solution to the O$_2$ diffusion model is an equation for PO$_2$ as a function of distance (x) from the choroid that is linear in nonconsuming regions (OS, ONL) and quadratic in the consuming region (IS). $P_e$ is the fitted PO$_2$ at the choroid-ROP boundary. $P_i$ is the fitted PO$_2$ at the inner-outlet retinal border (x = L), which was taken to be 50% of retinal depth. The main parameter derived from fitting is $Q_{on,O_2}$, the oxygen

![Figure 1. Oxygen profile data (dotted trace) with the outer retinal model fit (solid trace) superimposed. A simplified schematic of the retina is shown to illustrate the anatomic correspondence of each model layer.](http://arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932919/)
consumption of the outer half of the retina. $Q_{OR-02}$ was corrected to compensate for the differences in profile length, due to possible tissue distortions that may occur during electrode withdrawal, by multiplying the fitted $Q_{OR-02}$ by \( (1/x_{OR}) \), where $L$ is the outer retinal thickness, in micrometers, of the individual profiles, and $L_{OR}$ is the average thickness of many outer retinal profiles. $L_{OR}$ is the actual thickness of the outer retina, taken to be 100 μm in the current study, based on published data.\(^{13,14}\) A more detailed discussion of this correction factor can be found in Yancey and Linsenmeier.\(^{15}\) A satisfactory model fit to the data could not be obtained in one cat.

The fraction of photoreceptor oxygen delivered by the retinal circulation can also be calculated from the fitted parameters of the oxygen diffusion model. It is simply the ratio of the oxygen flux from the inner retina \( \left( \frac{dP_2}{dx_{12}} \right) \) divided by the total oxygen flux into layer 2 \( \left( \frac{dP_2}{dx_{11}} \right) + \left( \frac{dP_2}{dx_{12}} \right) \), where $P_2$ is the PO\(_2\) in layer 2 of the diffusion model.

Statistics

Individual profile values were averaged within cats to obtain an average parameter value for each cat. Two-tailed paired \( t \) tests were performed to determine whether there was a significant difference between control and altered conditions. This method ensured that data from each cat were weighted equally. \( P < 0.05 \) was defined as statistically significant. The average results from each cat were then averaged to obtain the overall average reported in this study. All data are reported as the mean ± SD.

**RESULTS**

**Effect of Acute Hyperglycemia on Outer Retinal PO\(_2\)**

Oxygen profiles through the dark-adapted retina during hyperglycemia were similar to those recorded during normoglycemia in this experimental series and those recorded earlier.\(^{14}\) Figure 2 shows sets of profiles recorded during normoglycemia and hyperglycemia in two cats. Oxygen diffuses down its concentration gradient from regions of high oxygen tension to regions of low oxygen tension. The outer retina is between retinal depths 50% and 100%, in which O\(_2\) consumption was confined to the photoreceptor IS. PO\(_2\), which was highest at the retinal–choroidal boundary (100% retinal depth, $x = 0$), decreased linearly through the OS layer ($Q_{OS-02} = 0$) to the mitochondria in the IS layer. Oxygen was also supplied by the retinal circulation, as indicated by the slope toward the IS layer from the inner–outer retinal boundary (50% thickness, $x = L$).

Photoreceptor (outer retinal) oxygen consumption \( Q_{OR-02}^{\text{ret}} \) did not significantly change when healthy cats were made acutely hyperglycemic (blood glucose >550 mg/dL) for several hours (average, 5.19 ± 0.83). The $Q_{OR-02}$ was 2.80 ± 1.00 mL O\(_2\)/100 g per minute during normoglycemia and 2.81 ± 0.91 mL O\(_2\)/100 g per minute during hyperglycemia ($n = 8$ cats). Figure 3 shows the average $Q_{OR-02}$ for each cat, as well as the averages across cats, during control and hyperglycemic conditions.

Oxygen tension \( (PO_2) \) at the inner/outer retinal boundary \( (L) \) increased in five of eight cats; however, the average was not significantly different during hyperglycemia \( (7.6 ± 3.4 \text{ mm Hg}) \) compared with control \( (6.2 ± 3.2 \text{ mm Hg}) \) conditions.

During hyperglycemia, the measured choroidal PO\(_2\) \( (P_c) \) decreased by an average of 5.8 ± 7.4 mm Hg, but by as much as 21.2 ± 21.2 mm Hg in one cat. Actual choroidal PO\(_2\) was 41.2 ± 16.2 mm Hg during normoglycemia and 35.4 ± 11.8 during hyperglycemia ($n = 9$, $P = 0.049$). Individual profiles demonstrating the hyperglycemia-induced decrease in choroidal PO\(_2\) are shown in Figure 2 for two cats. The normalized change in choroidal PO\(_2\), for each cat and the time course in one cat are shown in Figure 4. Because of the lowered choroidal PO\(_2\), a larger fraction of oxygen was delivered to the photoreceptors by the retinal circulation during hyperglycemia compared with normoglycemia. Figure 5 shows that the amount of oxygen delivered to the photoreceptors by the retinal circulation increased by 57% during hyperglycemia from 7.4% ± 5.9% during normoglycemia to 11.6% ± 6.3% during hyperglycemia ($P = 0.03$, $n = 8$).

Glucose was returned to the normal range in five cats. The recovery period lasted an average of 129 ± 95 minutes, during which time glucose averaged 123 ± 19 mg/dL. $Q_{OR-02}$ was not significantly different during hyperglycemia \( (2.47 ± 1.01 \text{ mL O}_2/100 \text{ g per minute}) \) and the recovery period \( (2.39 ± 0.91 \text{ mL O}_2/100 \text{ g per minute}) \) in these five cats. Choroidal PO\(_2\) did not recover during the recovery period \( (P_c = 32.5 ± 15.8 \text{ mm Hg during recovery}, P_c = 32.0 ± 13.5 \text{ mm Hg during hyperglycemia}) \).

**Effect of Acute Hyperglycemia on Inner Retinal PO\(_2\)**

The average inner retinal PO\(_2\) did not change significantly during hyperglycemia \( (12.1 ± 4.4 \text{ mm Hg}, n = 9) \) compared
with normoglycemia (12.5 ± 4.5 mm Hg, n = 9). Preretinal PO2 (0–100 μm away from the retinal surface) was also examined, with similar findings. In the 100 μm of vitreous adjacent to the retina, average PO2 was 15.6 ± 6.5 mm Hg during normoglycemia and 13.6 ± 5.8 mm Hg during hyperglycemia.

Data were recorded from five cats during the recovery period and also showed no significant change in average inner retinal PO2 or preretinal PO2 when blood glucose levels were returned to normal.

**DISCUSSION**

**Effect of Hyperglycemia on Outer Retinal PO2**

Because the Crabtree effect is controlled by availability of ADP and Pi, it should be observed early during hyperglycemia if it exists. Based on the in vivo quantification of photoreceptor oxygen consumption (QOR-O2) during normoglycemia and hyperglycemia that lasted several hours, it appears that the Crabtree effect does not occur to any significant degree in the outer retina. QOR-O2 was not significantly lower during hyperglycemia than under control conditions, even when blood glucose was very high (>500 mg/dL). This conclusion is supported by the findings of Wang et al. who measured the oxygen arteriovenous differences in the porcine choroid. They observed no evidence of a Crabtree effect with the blood glucose in the range of 10 to 25 mM (200–500 mg/dL). Also, we observed no change in photoreceptor glycolytic metabolism during acute hyperglycemia in a similar preparation from the cat.

There is some evidence that long-term hyperglycemia changes retinal metabolism, however. Illing and Gray and Sutherland et al. observed a decrease in oxygen consumption in the diabetic rabbit retina compared with normal animals. Because the rabbit retina is mostly avascular, total retinal consumption is representative of outer retinal (photoreceptor) oxygen consumption. Therefore, the results of the present study may indicate that decreased photoreceptor oxygen consumption in diabetes is a secondary change, rather than one resulting directly from hyperglycemia.

In the current work, QOR-O2 was lower than in some previous studies. The average QOR-O2 during normoglycemia was 3.03 ± 1.41 mL O2/100 g per minute compared with a range of 3.9 to 5.1 mL O2/100 g per minute in previous studies. This is most likely a direct result of Pcs being lower than usual in this study (40.9 ± 16.7 mm Hg vs. >60 mm Hg). In addition, the large variation of QOR-O2 in this study can be explained by the wide variation in Pcs. In agreement with previous work, QOR-O2 had a strong linear relationship with Pcs (Fig. 6).

Choroidal PO2 unexpectedly decreased further by an average of 11.4% during hyperglycemia, compared with control conditions in the present study. Why choroidal PO2 decreased during hyperglycemia is not understood. A decrease in choroidal PO2 is consistent with a lowered choroidal blood flow. Decreased choroidal lobular perfusion has also been observed in diabetic patients with no retinopathy. Intuitively, it might be concluded that a decrease in choroidal PO2 would result in an increased choroidal blood flow, but this is unlikely. The choroid does not regulate its blood flow in response to changes in PO2. In addition, increasing choroidal blood flow would not result in a significant increase in choroidal PO2.

The decrease in choroidal PO2 during hyperglycemia was not a general deterioration with time, but was related to blood glucose levels.
O2-saturation during hyperglycemia in diabetic persons with average inner retinal PO2, it seems that the increased reliance of the photoreceptor on the retinal circulation may be passively compensated by the retinal circulation that was related to the increased consumption of oxygen, and potentially other nutrients, from the retinal circulation to the outer retina. This may be partially because our method is not sensitive to very small changes in QORO2, but also that the O2 deficit from the decreased choroidal oxygen flux seemed to be made up by the retinal circulation. This was indicated by the 57% increase in photoreceptor oxygen derived from the retinal circulation (11.6% vs. 7.4%). Because the hyperglycemia-induced decrease in PpO2 did not correlate with an increase in average inner retinal PO2, it seems that the increased reliance of the photoreceptors on the inner retina was not a regulatory compensation by the retinal circulation that was related to the decreased choroidal PO2. Rather, the increased reliance of the photoreceptor on the retinal circulation may be passively related to the acidosis that occurs during acute hyperglycemia. One consequence of acidosis may be the 15% increase in retinal blood flow that occurs during hyperglycemia in cats.

Although our data did not reveal an increase in average inner retinal PO2 during hyperglycemia, which might have been expected with an increase in blood flow, we may have missed increases because inner retinal PO2 is variable and we could not record from identical locations before and during hyperglycemia. Tiedeman et al. observed a 12% decrease in retinal vein O2-saturation during hyperglycemia in diabetic persons with no retinopathy. They interpreted this as an increase in inner retinal oxygen consumption. We cannot rule out this explanation, but it is possible that in these subjects, choroidal PO2 decreased during hyperglycemia, as in this experimental series. If this was the case, an increased flux of oxygen from the retinal circulation to the photoreceptor could result in an increase in the oxygen delivered by the retinal circulation. We suggest that their results do not necessarily indicate an increase in total retinal oxygen consumption, but possibly a redistribution of oxygen, and potentially other nutrients, from the retinal circulation to the outer retina.

The 11.4% decrease in choroidal oxygen tension is probably reflective of a decrease in choroidal blood flow. Consistent with this conclusion, decreased choroidal lobular perfusion has been observed in diabetic patients, and one animal in a study in cats with long-term diabetes had a particularly low choroidal PO2 (PpO2 = 15.8 mm Hg). It should be mentioned, however, that Ernest and Goldstick reported a decreased choroidal vascular resistance during an abrupt increase in blood glucose to 1500 mg/dL for 30 minutes in the cat. Their observations may differ from ours, because the differences in time course and severity of hyperglycemia make the two studies incomparable. The mechanism by which hyperglycemia would change choroidal blood flow in either direction is not currently known.

Effect of Hyperglycemia on the Inner Retina

The effect of hyperglycemia on the inner retina was surprisingly small. Because average inner retinal PO2 did not change significantly, it is reasonable to suggest that hyperglycemia does not hinder autoregulation of inner retinal oxygen during air breathing. However during hyperoxia the situation may be different. Ernest et al. observed an increase in preretinal PO2 transients in response to breathing 100% O2 in both normal and diabetic dogs during hyperglycemia compared with normoglycemia. Similarly, Grunwald et al. found a smaller regulatory decrease in retinal blood flow in diabetic patients compared with age-matched normal subjects during hyperoxia.

Although short-term hyperglycemia did not produce inner retinal hypoxia, experimental diabetes is known to be accompanied by tissue hypoxia and altered oxygen flux from retinal arteries. The present work does not provide evidence on whether prolonged hyperglycemia per se or other pathologic effects secondary to prolonged hyperglycemia cause the hypoxia in diabetes. We have suggested previously that the activation of leukocytes and consequent plugging of retinal capillaries are among the important changes initiated by hyperglycemia that lead to tissue hypoxia.

In summary, photoreceptor oxidative metabolism and retinal oxygenation did not drastically change during acute episodes of hyperglycemia in the intact cat retina. These results, along with our study demonstrating retinal pH changes during hyperglycemia, concur with other studies that have failed to demonstrate a Crabtree effect in the outer retina.
conclude that short-term hyperglycemia does not lead directly to tissue hypoxia in the inner retina.

Acknowledgments

The authors thank Thomas K. Goldstick, Christina Enroth-Cugell, and Jennifer Kang Derwent for assistance during the experiments and useful discussions.

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