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# Do photoreceptor cells cause the development of retinal vascular disease?

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ABSTRACT

The retinal vasculature is affected in a number of clinically important retinopathies, including diabetic retinopathy. There has been a considerable amount of research into the pathogenesis of retinal microvascular diseases, but the potential contribution of the most abundant cell population in the retina, photoreceptor cells, has been largely overlooked. This review summarizes ongoing research suggesting that photoreceptor cells play a critical role in the development of retinal vascular disease in diabetic retinopathy and other retinopathies.



## 1. Introduction

The vasculature of the retina is adversely affected in a number of retinopathies, including diabetic retinopathy, retinopathy of prematurity, and also in retinal degenerations. In retinopathies where the vasculature is regarded as the central site of pathology (such as diabetic retinopathy (DR)), a central research focus to explain the visual dysfunction has been on the vasculature itself, but the potential contribution of photoreceptor cells (which account for most of the mass and metabolic activity of the retina) to the vascular disease has been largely overlooked. In genetic diseases that cause photoreceptor degeneration, in contrast, there has been great focus on the photoreceptor damage, but little interest in the retinal vasculature, even though the photoreceptor degeneration causes retinal capillaries to become damaged or degenerate (de Gooyer, Stevenson, Humphries, Simpson, Curtis, et al., 2006; Fernandez-Sanchez et al., 2012; Heegaard, Rosenberg, Preising, Prause, & Bek, 2003; Liu et al., 2016; Penn, Li, & Naash, 2000; Pennesi, Nishikawa, Matthes, Yasumura, & LaVail, 2008; de Gooyer, Stevenson, Humphries, Simpson, Gardiner, et al., 2006). In recent years, evidence has begun to accumulate implicating retinal photoreceptor cells in the pathogenesis of retinal vascular degeneration. The goal of this review is to summarize recent evidence suggesting that photoreceptor cells play a critical role in the development of retinal vascular disease in mouse models, by comparing DR (regarded clinically as a vascular disease) and models of photoreceptor degeneration. The discussion will focus primarily on rods, since rod photoreceptor cells are more prevalent than cones in the mammalian retina.

## 2. Retinal photoreceptor cells

Photoreceptors are the most abundant cell-type in the retina (Masland, 2001), and are the most metabolically active neuron in the central nervous system (Ames, Li, Heher, & Kimble, 1992), and contain at least 75% of total retinal mitochondria (Demontis, Longoni, & Marchiafava, 2002; Johnson et al., 2007; Krizaj & Copenhagen, 2002; Morgans, El Far, Berntson, Wassle, & Taylor, 1998; Yang, Basinger, Gross, & Wu, 2003). They serve a unique function in the body, absorbing light and turning it into electrical energy that results in sight. When photoreceptors are struck by a photon of light, *11-cis* retinal undergoes photoisomerization to *all-trans* retinal, initiating a signaling cascade that results in the closing of cGMP-gated ion channels, and hyperpolarization of the photoreceptor cell. Even though it is clearly recognized that these cells are metabolically active in light, they are active also in darkness, using ATP to maintain ion gradients. The oxygen demand in rods has been calculated to more than double during dark adaptation (Birol, Wang, Budzynski, Wangsa-Wirawan, & Linsenmeier, 2007).

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## 3. Photoreceptor cells and the retinal vasculature

Absorption of light by photoreceptors clearly affects the retinal vasculature under normal physiologic conditions. This is easily demonstrated by the rapid change in retinal vascular diameter after turning a light on and off (flicker) (Kern, 2014). This neurovascular coupling likely shows the response of the vasculature to changes in metabolic demand by photoreceptors and other retinal cells in the presence and absence of light, although there is evidence that light can directly influence the vasculature (Sikka et al., 2014).

The effect of photoreceptors on the development of vascular diseases in the retina has been less obvious. Two pieces of evidence, however, suggest an important role of retinal photoreceptor cells in the development and progression of retinal vascular disease:

### 3.1. Beneficial effects of photocoagulation

Laser photocoagulation has been known for many years to inhibit progression of advanced retinopathies including DR and age-related macular degeneration (Graham, Binz, Shen, Constable, & Rakoczy, 2006; Virgili & Bini, 2007). It has long been accepted that one mechanism by which this beneficial effect is mediated in ischemic retinas is at least in part by destroying significant numbers of photoreceptors and RPE cells, thus resulting in reduced oxygen consumption due to fewer photoreceptor cells. As a result, there is increased availability of oxygen for use by the remaining retinal cells. Since acute destruction of photoreceptor cells can inhibit the progression of these retinal vascular diseases, the data strongly suggests that photoreceptors are important in at least advanced stages of those diseases. Evidence from the ETDRS (Early Treatment of Diabetic Retinopathy Study) (Early Treatment Diabetic Retinopathy Study Research Group, 1991) indicates that photocoagulation has benefit also in somewhat earlier stages of DR, but how much earlier in the development of the retinopathy that photoreceptors contribute is not clear.

### 3.2. Degeneration of the retinal vasculature in photoreceptor-specific diseases

The retinal vasculature is attenuated in genetic diseases that affect only photoreceptors, including retinitis pigmentosa (Milam, Li, & Fariss, 1998), and degeneration of the retinal microvasculature has been detected also in mouse models of photoreceptor degeneration (de Gooyer, Stevenson, Humphries, Simpson, Curtis, et al., 2006; Feng et al., 2014; Liu et al., 2016; Penn et al., 2000). Since rhodopsin expression is unique for the photoreceptor cells, the studies in opsin-deficient or opsin-mutant animals clearly illustrate that photoreceptors can initiate dysfunction and degeneration of retinal capillaries (Fig. 1). The vascular loss in retinal degenerations has escaped widespread recognition, likely because photoreceptor degeneration is more serious under those circumstances.

The mechanism by which the absence or degeneration of retinal photoreceptor cells in diseases could cause degeneration of the retinal vasculature is only beginning to be considered. The studies by de de Gooyer, Stevenson, Humphries, Simpson, Curtis, et al. (2006) showed that opsin-deficient animals (whose photoreceptors had undergone degeneration as a consequence of the opsin deficiency) developed a significant reduction in vascular density, consistent with vaso-obliteration. Liu et al. (2016) compared two mouse models of photoreceptor degeneration (*opsin*$^{-/-}$ and *Rho*$^{P23H/P23H}$) and control C57Bl/5J mice, and showed that retinal capillary degeneration in the two opsin mutants was substantial while photoreceptors were still present, but slowed after the photoreceptors degenerated. Photoreceptor degeneration in the opsin mutants studied happened quickly (essentially all photoreceptors were lost by 3–4 months of age), and capillary degeneration likewise ensued rapidly in these animals, with a doubling of the number of degenerate capillaries within the first month of life (Liu et al., 2016). Thus, it was not the absence of photoreceptors that damaged the retinal vasculature, but the presence of "sick" or stressed photoreceptors that damaged the vasculature, likely by release of soluble factors from the stressed photoreceptor cells that directly or indirectly led to the capillary degeneration.

Both of the opsin mutants developed retinal oxidative stress and activation of leukocytes, which might have contributed to the development of the retinal vascular disease. Activated leukocytes have been shown by us to cause cytotoxicity to retinal endothelial cells (Du et al., 2015; Li et al., 2012; Liu, Tang, Lee, & Kern, 2015; Liu, Tang, Du, et al., 2015; Saliba et al., 2015; Talahalli et al., 2013; Tang et al., 2013; Tian et al., 2013; Veenstra, Tang, & Kern, 2013).

## 4. Do retinal photoreceptors contribute to vascular lesions of DR?

Merely because photoreceptor cells play a role in dysfunction and degeneration of retinal capillaries in severe degenerative retinopathies like those mentioned above, it is not necessarily certain that similar mechanisms cause vascular lesions in DR. Nevertheless, it has been recognized for years that the retinal vasculature is especially sensitive to diabetes, even in comparison to the vasculature of the embryologically similar brain (grey matter) (Kern & Engerman, 1996). This raises a possibility that something unique to the retina plays an important role in the pathogenesis of the spectrum of lesions regarded as characteristic of DR. Consistent with this, there is data specifically related to DR that suggests that photoreceptors play an important role in the development of at least early stages of DR.

### 4.1. Influence of photoreceptor degeneration on retinal vessel disease in diabetes

Compared to nondiabetic *Rho*$^{-/-}$ mice, de Gooyer, Stevenson, Humphries, Simpson, Gardiner, et al. (2006) reported that experimentally diabetic *Rho*$^{-/-}$ mice showed a significant survival of the retinal vasculature in both the peripheral and central retina. The authors concluded that loss of the outer retina reduced the severity of DR in that model. Feng et al. likewise reported that diabetes (in a ciliopathy-induced retinal degeneration rat) inhibited the vasoregression that occurred secondary to the photoreceptor degeneration (Feng et al., 2009). In contrast, other investigators studying the effects of diabetes on the opsin-deficient mouse, as well as a different mouse having mutant opsin knocked in (*Rho*$^{P23H/P23H}$), found that diabetes did not protect against the photoreceptor-mediated degeneration of the retinal microvasculature (Liu et al., 2016).

### 4.2. Absence of DR in diabetic patients having also retinitis pigmentosa

Results of a survey sent to a group of diabetic patients who also had retinitis pigmentosa (Arden, 2001) suggested that diabetics who also had retinitis pigmentosa (and therefore, photoreceptor degeneration) were protected from the development of DR. This study lacked the photographic documentation or systematic quantitation of retinopathy that is found in clinical trials, but it does provide supportive evidence for the hypothesis that photoreceptor cells play an important role in the development of DR. The postu-

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