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Review

Retinal degeneration and local oxygen metabolism

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Abstract

Vision loss due to various forms of outer retinal degeneration remains a major problem in clinical ophthalmology. Most retinal degenerations are precipitated by genetic mutations affecting the retinal pigment epithelium and sensory retina, but it is becoming increasingly evident that resultant metabolic changes within the retina may also contribute to the further progression of photoreceptor cell loss. In particular, a role for the local oxygen environment within the retina has been proposed. The correct balance between retinal oxygen supply and oxygen consumption in the retina is essential for retinal homeostasis, and disruption of this balance is a factor in many retinal diseases. In animal models of photoreceptor degeneration, manipulation of environmental oxygen levels has been reported to be able to modulate the rate of photoreceptor degeneration. Clinically, hyperbaric oxygen therapy has already been used in retinitis pigmentosa patients and other types of oxygen therapy have been proposed. It therefore seems appropriate to review our current understanding of the oxygen environment in the normal and degenerating retina, and to build a clearer picture of how the retinal oxygen environment can be modulated. We focus on techniques that have been, or may be, applied clinically, such as modulation of systemic oxygen levels and modulation of retinal oxygen metabolism by light deprivation.

Data from direct measurements of intraretinal oxygen distribution in rat models at different stages of photoreceptor degeneration will be reviewed. These models include the Royal College of Surgeons (RCS) rat, and the P23H rat model of outer retinal degeneration. Microelectrode based techniques have allowed the intraretinal oxygen distribution to be measured as a function of retinal depth under well-controlled systemic conditions at different stages of the degeneration process. Both models showed changes in the intraretinal oxygen distribution during the degenerative period, with the changes reflecting the gradual loss of oxygen metabolism of the degenerating photoreceptors. This results in higher than normal oxygen levels in the remaining outer retina and a significant alteration in the oxygen flux from the choroid to the inner retina. The maintenance of normal oxygen levels in the inner retina implies that inner retinal oxygen uptake is well preserved, and that there is also reduced oxygen input from the deeper capillary layer of the retinal circulation. Choroidal oxygen tension and the oxygen tension in the pre-retinal vitreous were unaffected at any of the time periods studied prior to, and during, the degeneration process. It is well known that both hypoxia and hyperoxia can cause neural cell stress and damage. Logically, any therapeutic intervention based on oxygen therapy should attempt to restore the oxygen environment of the remaining retinal cells to within the physiological range. Before any oxygen based therapies for the treatment of retinal degeneration should be seriously considered, the oxygen environment in the degenerating retina should be determined, along with clinically usable methods to restore the oxygen environment to the critical cell layers.

Keywords: oxygen; retinitis pigmentosa; RP; retinal degeneration; oxygen metabolism

1. Introduction

Retinal degeneration in its various forms is responsible for vision loss in a large number of young adults. Retinitis pigmentosa (RP) for example, has a prevalence about 1 in 4000 (Berson, 1993). The condition is currently incurable and there are no established treatments proven to slow down the degenerative process. This situation understandably leads to a desire to try almost any plausible therapy. However, wherever possible, any new intervention strategies should come under scientific scrutiny before being applied clinically.

Retinitis pigmentosa is characterised by a progressive loss of photoreceptors through mechanisms not yet fully understood. Subsequent to the photoreceptor loss there is

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both vascular and neural remodeling (Marc et al., 2003). The pathogenesis of retinal degeneration is complicated. The involvement of the genetic aspects is well established (Berson, 1993), but there is increasing evidence that environmental factors may also play a role (Stone et al., 1999). Although many retinal degenerations are precipitated by genetic mutations, it is unavoidable that the loss of photoreceptors themselves will induce metabolic changes in the remaining retina. A number of reviews deal with the genetic aspects of retinal degeneration (Berson, 1993; Dryja and Berson, 1995), but there is much less known about the environmental and metabolic aspects of the degenerative process.

Although it is well known that the retina is a high-energy demand tissue, studies on the possible roles of the metabolic microenvironment of the retina in retinal degeneration has not received much prior attention. Oxygen is known to be the most supply limited metabolite in the retina (Anderson and Saltzman, 1964), and there is limited evidence to suggest that retinal oxygen metabolism may be increased in RP patients (Anderson, 1968). Despite the lack of specific information about the role of oxygen in the degeneration process, manipulation of the oxygen environment of the retina has been proposed as an avenue for therapeutic intervention. Hyperoxia has been used to treat retinal degeneration clinically. Significant improvements have been reported in the electrophysiological responses in the treatment of retinitis pigmentosa patients with hyperbaric oxygen therapy (Vingolo et al., 1997, 1999). In animal models, hyperoxia has been shown to slow the rate of photoreceptor death during a 'critical period' in the early stage of retinal degeneration in RCS rats (Maslim et al., 1997; Valter et al., 1998) and in neonatal *rd* mice (Choi et al., 2001). However, later in the RCS rat model, hyperoxia has been shown to accelerate the degeneration, leading to a hypothesis of 'oxygen toxicity' being responsible for the final stages of photoreceptor degeneration (Valter et al., 1997; Stone et al., 1999). These observations from clinical and animal trials are difficult to reconcile, and point to significant gaps in our understanding of the role of oxygen in the degeneration process.

Perhaps the logical place to begin any discussion about the possible role of oxygen environment in retinal degenerations is to outline what we know about the normal oxygen environment, and how this is regulated in the healthy retina. We shall then move on to review what is known about the influence of photoreceptor loss on the oxygen environment in the remaining retina during the disease progression. We will review the changes in retinal oxygen metabolism in two animal models of retinal degeneration, the RCS and P23H rat, and provide quantitative evidence of changes in the oxygen environment and highlight the possible roles of altered retinal cellular metabolism in the pathogenesis of retinal degeneration. It is hoped that the results from animal models of retinal degeneration could provide relevant information for improving strategies for therapeutic intervention in the degeneration process. If oxygen therapy is ever to be adopted for routine treatment of RP then it is important to understand the relationship between environmental oxygen levels and its effect on intraretinal oxygen levels in both healthy and diseased eyes.

2. The oxygen environment in the healthy retina

In general terms, all of the vascularised retinas studied to date have a similar oxygen distribution as a function of depth through the different retinal layers. This intraretinal oxygen distribution reflects the combined effects of the discrete sources of oxygen and the oxygen consumption rates of the different cell classes from which the retina is composed. Oxygen supply to the retina is derived from two separate vascular systems. The choroid provides oxygen to the outer retina, whilst the retinal circulation provides the oxygen requirements of the inner retina through which the retinal circulation passes. The properties of the retinal and choroidal circulations are remarkably different. The retinal circulation is relatively sparse (presumably to allow passage of light to the photoreceptors), with a high arteriovenous oxygen difference, and well-developed autoregulatory mechanisms. In contrast, the choroid is highly vascularized, has a small arteriovenous oxygen difference, and demonstrates little autoregulatory response to oxygen perturbation. Understanding these physiological properties of the two circulations supplying the retina is crucial in predicting the response of the retina to environmental manipulation of systemic oxygen levels. An equally important issue, however, is to understand the heterogeneous nature of oxygen distribution and consumption in the various retinal layers, and how this is influenced by oxygen availability. For many years it has been known that outer retinal oxygen consumption is dominated by the inner segments of the photoreceptors (Linsenmeier, 1986). The avascular nature of the outer retina means that it is particularly vulnerable to changes in oxygen supply or demand. We shall restrict our discussion to the rat retina, as this species has perhaps received the most attention in animal models of retinal degeneration. The normal oxygen distribution across the rat retina has been studied previously (Yu et al., 1994) and an example of the intraretinal oxygen distribution is shown in Fig. 1. The example shows intraretinal oxygen profiles measured under light adapted and dark adapted conditions at the same retinal location. Consider for the moment only the light adapted data. The first point to note is that the oxygen levels in different retinal layers are markedly heterogenous. The highest oxygen levels are found in the choroid, but this falls dramatically across the outermost retina, creating a large gradient of oxygen towards the inner segments of the photoreceptors. The rapid change in oxygen gradient in this region ($\sim$320 μm penetration depth) reflects the high oxygen consumption of the inner segments. A plateau