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ABSTRACT

Retinopathy of prematurity (ROP) is a neurovascular disease that affects prematurely born infants and is known to have significant long term effects on vision. We conducted the studies described herein not only to learn more about vision but also about the pathogenesis of ROP. The coincidence of ROP onset and rapid developmental elongation of the rod photoreceptor outer segments motivated us to consider the role of the rods in this disease. We used noninvasive electroretinographic (ERG), psychophysical, and retinal imaging procedures to study the function and structure of the neurosensory retina. Rod photoreceptor and post-receptor responses are significantly altered years after the preterm days during which ROP is an active disease. The alterations include persistent rod dysfunction, and evidence of compensatory remodeling of the post-receptor retina is found in ERG responses to full-field stimuli and in psychophysical thresholds that probe small retinal regions. In the central retina, both Mild and Severe ROP delay maturation of parafoveal scotopic thresholds and are associated with attenuation of cone mediated multifocal ERG responses, significant thickening of post-receptor retinal laminae, and dysmorphic cone photoreceptors. These results have implications for vision and control of eye growth and refractive development and suggest future research directions. These results also lead to a proposal for noninvasive management using light that may add to the currently invasive therapeutic armamentarium against ROP.

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1. Introduction

1.1. Preterm birth and retinopathy of prematurity (ROP)

Retinopathy of prematurity (ROP), which afflicts infants born before term, is characterized by abnormal retinal vasculature at preterm ages. ROP onset occurs when the neurosensory retina is quite immature. The photoreceptors are the last cells to complete maturation. Term is at 40 weeks, approximately 9 months, gestation. No matter the gestational age at birth, and no matter the ultimate severity of the retinopathy, the onset of ROP is at approximately 32 weeks gestation; that is, 32 weeks after the mother's last menstruation. At this age, the developmental increase in the rhodopsin content of the retina escalates, as shown in Fig. 1. The developmental increase in rhodopsin (Fulton et al., 1999a), consequent to the increasing elongation of the rhodopsin bearing rod outer segments, lags the normal vascular coverage of the peripheral retina. The course of active ROP is quite brief; ROP typically resolves in the early post term weeks (Repka et al., 2000).

The coincidence of ROP onset and rod outer segment development motivated us to consider the rods as a major player in the pathogenesis of ROP. What if the developing rod outer segments' burgeoning energy demands to support the circulating current (Ames et al., 1992), turnover of outer segments (Tamai and Chader, 1979), and phototransduction drove the retinal hypoxia that stimulated the abnormal ROP vasculature? This question led us to design and perform experiments in rat models of ROP and in preterm born infants and children that would test the relationships among the neurosensory retina, its vascular supply, and even the development of the eye as a whole.

This paper is about our studies of human ROP subjects. First we briefly summarize results from rat models of ROP that are pertinent to the interpretation of data from human subjects. Our use of noninvasive techniques facilitates translation between species.

In a rat model, retinopathy is induced by exposure of newborn pups with immature retina to alternating high and low levels of ambient oxygen. In the ROP rat, we found that deficits in the rod photoresponse calculated from the a-wave of the electroretinogram (ERG) antedated the appearance of abnormal retinal vasculature (Reynaud et al., 1995). Specifically, the kinetics of activation of rod phototransduction were slower and indicative of lower sensitivity, and the amplitude of the saturated response was smaller than in controls. While delayed development of the ROP rods could explain low sensitivity and small amplitude, the total amount of rhodopsin extracted from control and ROP rat retina did not differ significantly; this is not consistent with a mere delay in development of the rods but rather suggests dysfunction of the rods (Dodge et al., 1996; Fulton et al., 1995). By microspectrophotometry (MSP), the transverse density of the rhodopsin in the ROP rod outer segments was significantly more variable than in controls. The total rhodopsin content of the retina, calculated from the MSP data, was in good agreement with the rhodopsin content obtained by quantitative extraction of the whole retina (Dodge et al., 1996). Furthermore, by electron microscopy, the outer and inner segments of the ROP rods were disorganized and dysmorphic (Fulton et al., 1999b). Thus, the ROP rats had functional and structural evidence of hypoxic and hyperoxic injury induced by ambient conditions (Barnett et al., 2010; Dodge et al., 1996; Liu et al., 2006a; Madan and Penn, 2003; Penn et al., 1994; Reynaud et al., 1995; Roberto et al., 1996; Shao et al., 2011). It has since been confirmed that both hypoxia and hyperoxia are injurious to the immature rods (Wellard et al., 2005).

The choroidal vasculature, which is the main supplier of oxygen to the rods, may play a role in photoreceptor injury. The choroid is thin in ROP rats (Shao et al., 2011). Due to the choroid's

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