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The neurovascular retina in retinopathy of prematurity

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A B S T R A C T

The continuing worldwide epidemic of retinopathy of prematurity (ROP), a leading cause of childhood visual impairment, strongly motivates further research into mechanisms of the disease. Although the hallmark of ROP is abnormal retinal vasculature, a growing body of evidence supports a critical role for the neural retina in the ROP disease process. The age of onset of ROP coincides with the rapid developmental increase in rod photoreceptor outer segment length and rhodopsin content of the retina with escalation of energy demands. Using a combination of non-invasive electroretinographic (ERG), psychophysical, and image analysis procedures, the neural retina and its vasculature have been studied in prematurely born human subjects, both with and without ROP, and in rats that model the key vascular and neural parameters found in human ROP subjects. These data are compared to comprehensive numeric summaries of the neural and vascular features in normally developing human and rat retina. In rats, biochemical, anatomical, and molecular biological investigations are paired with the non-invasive assessments. ROP, even if mild, primarily and persistently alters the structure and function of photoreceptors. Post-receptor neurons and retinal vasculature, which are intimately related, are also affected by ROP; conspicuous neurovascular abnormalities disappear, but subtle structural anomalies and functional deficits may persist years after clinical ROP resolves. The data from human subjects and rat models identify photoreceptor and post-receptor targets for interventions that promise improved outcomes for children at risk for ROP.

Contents

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1. Introduction

1.1. Preterm birth and retinopathy of prematurity (ROP)

Preterm birth introduces a tiny infant into an extrauterine world for which the infant's tissues and organs are incompletely prepared. In this external environment, the immature neurovascular tissues of the visual system, the retina and the brain, are particularly susceptible to injury (Volpe, 2009). The earlier the preterm birth, the greater the risk for damage to the retina and visual pathways. The clinical entity involving the retina is called retinopathy of prematurity (ROP); abnormalities of the retinal vasculature are the clinical hallmark of ROP. A growing body of evidence, however, demonstrates that the neural retina is critically involved in the ROP disease process. The onset of ROP is at approximately 32 weeks gestational age (term $\cong$40 weeks) regardless of the gestation at birth (Palmer et al., 1991). Interestingly, this coincides with the rapid developmental elongation of the rod outer segments and increase in retinal rhodopsin content (Fig. 1). As this rapid maturation occurs, putative energy demands of the rod escalate due to increase in turnover of outer segment material and the rod's circulating current.

Our studies of ROP are dedicated to delineating the closely allied neural and vascular components of the disease and the resulting retinal and visual dysfunction. Such an approach can identify targets for interventions that will give children with ROP the best possible visual outcome. The increasing number of children with ROP motivates the quest for further knowledge about neurovascular processes upon which improved management, and eventually prevention, of ROP will be based.

Due to advances in neonatal care, infants born as early as 22–24 weeks gestation survive. Each year in the United States, an estimated 10,000 infants are born prematurely (Penn et al., 2008). Of those born extremely prematurely (gestational age <31 weeks or birth weight <1250 g), approximately half develop ROP. In the majority, the disease is mild and resolves spontaneously. Nonetheless, ROP remains a leading cause of permanent, bilateral visual impairment in developed countries (Steinkuller et al., 1999). An estimated 1100 to 1500 each year have severe ROP that requires treatment, and approximately 500 of these infants are blinded by ROP (www.nei.nih.gov/health/rop). Worldwide, a hundred times that number are blind from ROP (Gilbert, 2008). The risk of ROP blindness is particularly high in middle income countries where premature infants survive but screening programs for ROP or management of ROP are not well established (Gilbert, 2008). Although in countries with advanced neonatal care and established screening programs, the rates of retinal detachment and blindness due to ROP are quite low, even mild ROP causes residual retinal and visual dysfunction (Reisner et al., 1997; Hansen and Fulton, 2000b; Fulton et al., 2001; O'Connor et al., 2002a; Barnaby et al., 2007; Hammer et al., 2008).

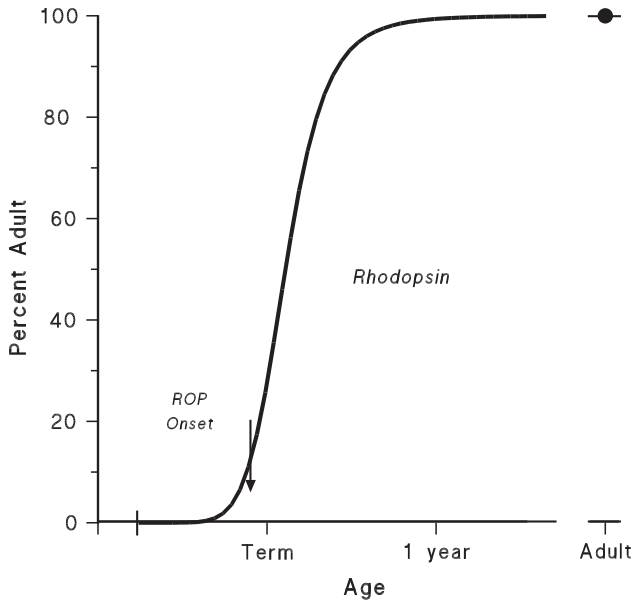

Fig. 1. Human rhodopsin growth curve and ROP onset. The smooth curve is normalized to the median adult rhodopsin content, 7.19 nmol/retina (Fulton et al., 1999a). Rhodopsin content reached 50% of the adult value at 5 weeks post-term (95% confidence interval: 0–10 weeks). The arrow indicates the age of ROP onset (technically pre-threshold ROP) at 32 weeks gestational age (Palmer et al., 1991). ROP onset coincides with a period of rapid developmental increase in rhodopsin content.