Chapter 8

HYPOXIA AND RETINAL NEOVASCULARIZATION

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Abstract: For over 50 years, retinal hypoxia has been considered to be a major causative factor in the development of retinal neovascularization (NV), a condition associated with blindness and vision loss in a variety of retinopathies. Review of the existing literature and results of new experiments from our laboratory strongly suggest that the oxygen-based pathophysiology stimulating retinal NV is more complicated than previously thought. Our evidence identifies at least two independent conditions involved in the pathogenesis of retinal NV: hypoxia measured under steady-state conditions (i.e., static hypoxia) and found at the border of vascular and avascular retina, and subnormal oxygenation response measured during a provocation and found over both vascular and avascular retina. In practical terms, the identification of links between static hypoxia, oxygen supply dysfunction and NV may lead to improved therapeutic strategies for preventing vision loss and blindness from retinal NV.

1. INTRODUCTION

Normally, retinal vessels develop in utero by two mechanisms: vasculogenesis (formation of vessels from precursor cells) and angiogenesis (sprouting of vessels from the existing circulation). The inner (or superficial) circulation develops first, largely via vasculogenesis, and covers the retina by about week 26 post-conception. Outer (or deep net) vessel development lags behind that of the inner circulation and is mostly complete by birth. Under special circumstances, a third form of new retinal vessel growth also occurs. In this case, poorly formed blood vessels abnormally grow from the...
existing circulation through the inner limiting membrane and into the vitreous and are subsequently associated with vision loss and blinding complications in retinopathies such as diabetic retinopathy and retinopathy of prematurity (ROP). This ocular pathological angiogenic process is termed neovascularization (NV).

The development of all three forms of retinal vessels is commonly thought to occur when oxygen supply is inadequate to meet demand during resting conditions, or hypoxia. The retina is one of the most metabolically active tissues in the body, and it has a very high oxygen demand. Because oxygen is not stored within retinal tissue, a continuous supply of oxygen is necessary to maintain adequate retinal nutrition. Consequently, oxygen supply and demand must be precisely balanced through active regulation of nutrient delivery and waste removal to ensure the health of the retina. Retinal hypoxia can occur, for example, during a retinal ischemic event (e.g., branch retinal artery occlusion) in which oxygen supply stops but oxygen consumption is not downregulated.

Historically, this hypoxia hypothesis (Figure 1) evolved from the initial work of Michaelson in 1948. He studied excised, India ink-injected pre- and postnatal retinas and noted that there were large capillary-free zones around arteries and that capillary growth tended to occur on the side of the vein farthest from the artery. Presumably, these avascular regions were receiving adequate amounts of oxygen from arteries relative to demand. Michaelson hypothesized that in the development of embryonic retinal vessels, and possibly for NV, oxygen concentration gradients from well to poorly oxygenated retina (e.g., from artery to vein) regulated a factor “X,” which in turn influenced new vessel development. Furthermore, subsequent work by others showed that as the inspired oxygen fraction increased or decreased, the size of the capillary-free zones around arteries widened or narrowed, respectively. In support of Michaelson’s hypothesis, Chan-Ling et al. examined normal retinal vessel development in kittens by measuring the extent of vasculogenic cell division. Cell division was found to be inversely proportional to the level of oxygen in the inspired gas mixture, and they speculated that a “physiological” level of hypoxia related to increased retinal neuronal demand stimulates vasculogenesis.