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Retinovascular physiology and pathophysiology: New experimental approach/new insights

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ABSTRACT

An important challenge in visual neuroscience is to understand the physiology and pathophysiology of the intra-retinal vasculature, whose function is required for ophthalmoception by humans and most other mammals. In the quest to learn more about this highly specialized portion of the circulatory system, a newly developed method for isolating vast microvascular complexes from the rodent retina has opened the way for using techniques such as patch-clamping, fluorescence imaging and time-lapse photography to elucidate the functional organization of a capillary network and its pre-capillary arteriole. For example, the ability to obtain dual perforated-patch recordings from well-defined sites within an isolated microvascular complex permitted the first characterization of the electrotonic architecture of a capillary/arteriole unit. This analysis revealed that this operational unit is not simply a homogenous synctium, but has a complex functional organization that is dynamically modulated by extracellular signals such as angiotensin II. Another recent discovery is that a capillary and its pre-capillary arteriole have distinct physiological differences; capillaries have an abundance of ATP-sensitive potassium (K_{ATP}) channels and a dearth of voltage-dependent calcium channels (VDCCs) while the converse is true for arterioles. In addition, voltage transmission between abluminal cells and the endothelium is more efficient in the capillaries. Thus, the capillary network is well-equipped to generate and transmit voltages, and the pre-capillary arteriole is well-adapted to transduce a capillary-generated voltage into a change in abluminal cell calcium and thereby, a vasomotor response. Use of microvessels isolated from the diabetic retina has led to new insights concerning retinal vascular pathophysiology. For example, soon after the onset of diabetes, the efficacy of voltage transmission through the endothelium is diminished; arteriolar VDCCs are inhibited, and there is increased vulnerability to purinergic vasotoxicity, which is a newly identified pathobiological mechanism. Other recent studies reveal that K_{ATP} channels not only have an essential physiological role in generating vasomotor responses, but their activation substantially boosts the lethality of hypoxia. Thus, the pathophysiology of the retinal microvasculature is closely linked with its physiology.

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1. Introduction

1.1. Retinal vasculature: unique task/unique adaptations

The circulatory system of the retina has the unique task of supplying oxygen and nutrients to a tissue whose translucency is essential for function. Throughout much of evolution, the metabolic needs of the vertebrate retina were met by the diffusion of nutrients and oxygen from the choriocapillaris, which is a dense vascular complex located beneath the retina and thus, not in the path of light passing to the photoreceptors. However, because an exclusive dependence on diffusion limits how far away neurons of the inner retina can be from the choriocapillaris, avascular retinas must be relatively thin (Chase, 1982; Buttery et al., 1991).

In contrast to sub-mammalian retinas, the retinas of most mammals and all primates contain blood vessels. By eliminating the exclusive dependence on the choriocapillaris, vascularized retinas are able to process visual information with a significantly thicker inner synaptic layer (Chase, 1982; Buttery et al., 1991). On the other hand, because intra-retinal blood vessels deflect incoming photons, they can compromise visual function. As a likely adaptation to limit blood vessel-induced image degradation, the density of capillaries in the retina is particularly low (Funk, 1997). However, this paucity of microvessels leaves little functional reserve for the vital task of adjusting local perfusion to meet the stringent metabolic demands of retinal neurons. Thus, it is particularly important that blood flow in the retina be especially tightly coupled to local needs.

Specialized adaptations enhance the ability of the retinal vasculature to effectively match blood flow to meet local metabolic needs despite having a low capillary density. One important adaptive feature of the retina's circulatory system is its functional independence. Another important feature is its highly decentralized functional organization.

The ability of the retinal vasculature to function independently is established, in part, by its tight blood-retinal barrier, which prevents circulating vasoactive molecules from directly affecting the contractile cells located on the blood vessel wall. Independence is also enhanced by the retinal vasculature's lack of autonomic innervation (Ye et al., 1990), which in other vascular beds, conveys CNS oversight of local blood flow. As a consequence of these adaptations, retinal blood flow is largely autoregulated and thus, is not subject to being diminished due to the metabolic demands of non-retinal tissues.

In addition to being autoregulated, the retinal vasculature has a highly decentralized functional organization that facilitates the efficient coupling of local perfusion to local needs. Indicative of its decentralized organization, the retina's circulatory system, unlike that of other tissues, consists exclusively of microvessels, i.e., arterioles and capillaries. Also consistent with a highly developed decentralized operation, the capillaries of the retina are reported to have the highest density of pericytes (Shepro and Morel, 1993), whose contractions and relaxations are thought to regulate local perfusion by altering the capillary lumen (Anderson, 1996; Funk, 1997; Peppiatt et al., 2006; Puro, 2007; Hamilton et al., 2010; Bonkowski et al., 2011). In addition, evidence is emerging that a capillary network plus its pre-capillary tertiary arteriole constitute an operational unit that is well adapted to regulate local perfusion at this decentralized location within the retinal vasculature (Oku et al., 2001; Matsushita et al., 2010; Zhang et al., 2011).

1.2. Research questions

Because visual function in humans, sub-human primates and most mammals is dependent on the proper functioning of the intra-retinal vasculature, an important research quest is to understand the physiology and pathophysiology of this portion of the circulatory system. Importantly, due to the specialized adaptations of the retinal vasculature, an understanding of how it functions in health and disease cannot be derived simply by extrapolating findings from the study of non-retinal blood vessels. Rather, the circulatory system of the retina must be analyzed in its own right.

Due to the importance of the retinal vasculature, it has received the attention of many talented investigators whose efforts have resulted in a substantial literature that has significantly advanced understanding (Schonfelder et al., 1998; Clermont and Bursell, 2007; Metea and Newman, 2007; Scholfield et al., 2007; Pournaras et al., 2008; Hamilton et al., 2010; Hein et al., 2010). However, because this review is a highly selective assessment focusing exclusively on physiological and pathophysiological studies of the most distal portion of the retinal microvasculature, i.e. the capillary/pre-capillary