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Metabolic physiology in age related macular degeneration☆

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A B S T R A C T

Ischemia and hypoxia have been implicated in the pathophysiology of age related macular degeneration (AMD). This has mostly been based on studies on choroidal perfusion, which is not the only contributor to retinal hypoxia found in AMD eyes. Other features of AMD may also interfere with retinal oxygen metabolism including confluent drusen, serous or hemorrhagic retinal detachment, retinal edema and vitreoretinal adhesion. Each of these features contributes to retinal hypoxia: the drusen and retinal elevation by increasing the distance between the choriocapillaris and retina; vitreoretinal adhesion by reducing diffusion and convection of oxygen towards and vascular endothelial growth factor (VEGF) away from hypoxic retinal areas. Hypoxia-inducible-factor is known to exist in subretinal neovascularization and hypoxia is the main stimulus for the production of VEGF. Each feature may not by itself create enough hypoxia and VEGF accumulation to stimulate wet AMD, but they may combine to do so.

Choroidal ischemia in AMD has been demonstrated by many researchers, using different technologies. Choroidal ischemia obviously decreases oxygen delivery to the outer retina.

Confluent drusen, thickening of Bruch's membrane and any detachment of retina or retinal pigment epithelium, increases the distance between the choriocapillaris and the retina and thereby reduces the oxygen flux from the choroid to the outer retina according to Fick's law of diffusion. Retinal elevation and choroidal ischemia may combine forces to reduce choroidal oxygen delivery to the outer retina, produce retinal hypoxia. Hypoxia leads to production of VEGF leading to neovascularization and tissue edema. A vicious cycle may develop, where VEGF production increases effusion, retinal detachment and edema, further increasing hypoxia and VEGF production.

Adhesion of the viscous posterior vitreous cortex to the retina maintains a barrier to diffusion and convection currents in the vitreous cavity according to the laws of Fick's, Stokes–Einstein and Hagen–Poiseuille. If the vitreous is detached from the surface of the retina, the low viscosity fluid transports oxygen and nutrients towards an ischemic area of the retina, and cytokines away from the retina, at a faster rate than through attached vitreous gel. Vitreoretinal adhesion can exacerbate retinal hypoxia and accumulation of cytokines, such as VEGF. Vitreoretinal traction can also cause hypoxia by retinal elevation.

Conceivably, the basic features of AMD, drusen, choroidal ischemia, and vitreoretinal adhesion are independently determined by genetics and environment and may combine in variable proportions. If the resulting hypoxia and consequent VEGF accumulation crosses a threshold, this will trigger effusion and neovascularization.

Contents

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1. Introduction

The pathophysiology of age related macular degeneration (AMD) is one of the major issues in eye research today. Genetic studies have pointed towards an inflammatory component, some clinical trials towards oxidative stress, while physiological studies have suggested that ischemia and hypoxia plays a role (Algvere et al., 2006; Bressler, 2009; Campochiaro, 2004; Curcio et al., 2009; Ding et al., 2009; Feigl, 2009).

Hypoxia-inducible-factor has been shown to be present in subretinal choroidal neovascular membranes (Inoue et al., 2007; Sheridan et al., 2009). Hypoxia in retinal cell cultures induces vascular endothelial growth factor (VEGF) (Aiello et al., 1995). Animal models of neovascularization show increased levels of vascular endothelial growth factor in hypoxia, and these increased levels correlated with the resultant neovascularization (Dorey et al., 1996).

Many mechanisms may be involved and they may contribute at different stages in the development of the disease. We will review the evidence pointing towards disturbances in blood flow and oxygen metabolism and propose a theory on the metabolic pathophysiology of AMD. Several independent observations pointing in this direction must be considered together to comprehend their true potential to alter retinal oxygen metabolism.

As early as 1937, Verhoeff and Grossman (1937) attributed the pathogenesis of AMD to impairment of choroidal blood flow and the development of drusen. Friedman et al. (1963) studied the relationship between drusen and the choriocapillaris. Friedman (2008) proposed that the etiology of AMD is largely attributable to impairment of choroidal perfusion.

The data pointing most directly towards ischemia are measurements of choroidal blood flow, which is disturbed during the development of AMD and may cause hypoxia and impaired energy metabolism in the retina. The aim of this essay is to point out that some other features of AMD, such as drusen and retinal elevation may also disturb the delivery of oxygen and nutrients from the choroid to the retina, simply by increasing the diffusion distance. Tissue edema and cystoid spaces may also increase diffusion distance from choroidal or retinal blood vessels to individual retinal cells. Finally, vitreoretinal adhesion, which has lately been proposed instrumental in the development of wet AMD may also limit the transvitreal delivery of oxygen to the retina and cytokine clearance. The fact that all of these components of AMD potentially influence oxygen delivery, cytokine production and clearance, makes a metabolic hypothesis for the pathogenesis of neovascular AMD more credible (Fig. 1). We will discuss these issues in detail and try to shed light on the pathophysiology of AMD, in particular the development of wet AMD.

2. Choroidal ischemia

2.1. Choroidal watershed zones and neovascularization

Hayashi and de Laey (1985) studied choroidal circulation by means of fluorescein and indocyanine green (ICG) angiography. In 10 cases with disciform response, they noticed that this was associated with either watershed zones of the choroidal circulation or with areas of choroidal circulatory disturbance. They concluded that this is consistent with the theory that hypoxic regions of the choroid are the underlying cause of macular disciform response. Recently, Mendrinos and Pournaras (2009) confirmed Hayashi and de Laey's observation and reported that choroidal neovascularization in exudative AMD occurred within the watershed zones in 44 of 50 patients (88%). Also using angiography, Goldberg et al. (1998) observed that most cases of choroidal neovascularization in AMD are localized close to areas with poor choroidal perfusion on indocyanine green angiography. Pauleikhoff et al. (1999) found prolonged choroidal filling phase as seen on fluorescein and indocyanine green angiography to be a common feature in patients with early AMD. Similar findings were reported by Piguet et al. (1992). Patients with AMD were more likely to have choroidal watershed filling defects during fluorescein (Chen et al., 1992) and indocyanine green angiography (Pauleikhoff et al., 1999; Ross et al., 1998; Ryan et al., 2001) than were controls, although the controls were not matched on important factors such as hypertension (Pauleikhoff et al., 1999; Ross et al., 1998).