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Progress in Retinal and Eye Research 24 (2005) 183–215
Progress in RETINAL AND EYE RESEARCH
www.elsevier.com/locate/prer

Visually evoked hemodynamical response and assessment of neurovascular coupling in the optic nerve and retina

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Abstract

The retina and optic nerve are both optically accessible parts of the central nervous system. They represent, therefore, highly valuable tissues for studies of the intrinsic physiological mechanism postulated more than 100 years ago by Roy and Sherrington, by which neural activity is coupled to blood flow and metabolism. This article describes a series of animal and human studies that explored the changes in hemodynamics and oxygenation in the retina and optic nerve in response to increased neural activity, as well as the mechanisms underlying these changes. It starts with a brief review of techniques used to assess changes in neural activity, hemodynamics, metabolism and tissue concentration of various potential mediators and modulators of the coupling. We then review: (a) the characteristics of the flicker-induced hemodynamical response in different regions of the eye, starting with the optic nerve, the region predominantly studied; (b) the effect of varying the stimulus parameters, such as modulation depth, frequency, luminance, color ratio, area of stimulation, site of measurement and others, on this response; (c) data on activity-induced intrinsic reflectance and functional magnetic resonance imaging signals from the optic nerve and retina. The data undeniably demonstrate that visual stimulation is a powerful modulator of retinal and optic nerve blood flow. Exploring the relationship between vasoactivity and metabolic changes on one side and corresponding neural activity changes on the other confirms the existence of a neurovascular/neurometabolic coupling in the neural tissue of the eye fundus and reveals that the mechanism underlying this coupling is complex and multi-factorial. The importance of fully exploiting the potential of the activity-induced vascular changes in the assessment of the pathophysiology of ocular diseases motivated studies aimed at identifying potential mediators and modulators of the functional hyperemia, as well as conditions susceptible to alter this physiological response. Altered hemodynamical responses to flicker were indeed observed during a number of physiological and pharmacological interventions and in a number of clinical conditions, such as essential systemic hypertension, diabetes, ocular hypertension and early open-angle glaucoma. The article

Abbreviations: ERG, electroretinogram; 1F, fundamental harmonic component of the flicker ERG; 2F, second harmonic component of the flicker ERG; LDF, laser Doppler flowmetry; RBCs, red blood cells; DSPS, Doppler shift power spectrum; *Vel*, blood velocity measured by LDF; *Vol*, blood volume; *F*, blood flow; DC, direct current of the LDF signal; F_{bl}, average value of *F* during baseline; F_{fl}, average value of *F* during the last 20 s of flicker; *RVel*, response of *Vel* to stimulus; *RVol*, response of *Vol* to stimulus; *RF*, response of *F* to stimulus; BLDV, bi-directional laser Doppler velocimetry; V_{max}, maximal (centerline) velocity of RBCs in a retinal vessel; SLDF, scanning laser Doppler flowmetry; HRF, Heidelberg retinal flowmeter; BFS, blue field simulation; WBCs, white blood cells; V_{WBC}, average speed of WBCs; D_{WBC}, average density of WBCs; RV_{WBC}, response of V_{WBC} to stimulus; *D*, diameter of retinal vessel; *RD*, response of *D* to stimulus; RD_{WBC}, response of D_{WBC} to stimulus; RVA, retinal vessel analyzer; pO_2, partial pressure of oxygen; R_pO_2, response of pO_2 to stimulus; τ, lifetime of the phosphorescence in the presence of oxygen; τ_o, lifetime of the phosphorescence in the absence of oxygen; k_q, phosphorescence quenching constant; NO, nitric oxide; *RNO*, response of NO to stimulus; BOLD, blood oxygen level dependent; CV, coefficient of variation; *Md*, modulation depth; L_{min}, minimum luminance level; L_{max}, maximum luminance level; CFF, critical flicker frequency; *r*, color ratio; PERG, pattern electroretinogram; $[K^+]$, concentration of potassium; $R[K^+]$, response of $[K^+]$ to stimulus; PP_m, mean ocular perfusion pressure; OHT, ocular hypertensive; EOAG, early open-angle glaucoma; MD, perimetric mean deviation

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1350-9462/$ - see front matter
doi:10.1016/j.preteyeres.2004.07.002

concludes with a discussion of key questions that remain to be elucidated to increase our understanding of the physiology of ocular functional hyperemia and establish the importance of assessing the neurovascular coupling in the diagnosis and management of optic nerve and retinal diseases.

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