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Review

MRI of rod cell compartment-specific function in disease and treatment *in vivo*

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ABSTRACT

Rod cell oxidative stress is a major pathogenic factor in retinal disease, such as diabetic retinopathy (DR) and retinitis pigmentosa (RP). Personalized, non-destructive, and targeted treatment for these diseases remains elusive since current imaging methods cannot analytically measure treatment efficacy against rod cell compartment-specific oxidative stress *in vivo*. Over the last decade, novel MRI-based approaches that address this technology gap have been developed. This review summarizes progress in the development of MRI since 2006 that enables earlier evaluation of the impact of disease on rod cell compartment-specific function and the efficacy of anti-oxidant treatment than is currently possible with other methods. Most of the new assays of rod cell compartment-specific function are based on endogenous contrast mechanisms, and this is expected to facilitate their translation into patients with DR and RP, and other oxidative stress-based retinal diseases.

Contents

Abbreviations: ADC, apparent diffusion coefficient; Arr1, Arrestin 1; ASL, arterial spin labeling; BRB, blood retinal barrier; BOLD, blood-oxygen level dependent; Cx36, connexin 36; Cx57, connexin 57; DIL, D-cis-diltiazem; DR, diabetic retinopathy; ERG, electroretinogram; HC, horizontal cell; IS, inner segments; MEMRI, manganese-enhanced MRI; OCT, optical coherence tomography; ONL, outer nuclear layer; RPE, retinal pigment epithelium; RP, retinitis pigmentosa; 1/T1r, spin-lattice relaxation rate in the rotating-frame; SRS, subretinal space; LTCCs, voltage-gated L-type calcium channels; wt, wildtype.

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1. Introduction

The most prevalent photoreceptor in the mammalian retina is the rod cell. Rod cells play an essential role in both vision and health of other cells in the retina (Berkowitz et al., 2014; Bissig et al., 2013; Cingolani et al., 2006; Curcio et al., 1996; Dong et al., 2006; Du et al., 2013; Kassen et al., 2009; Kolesnikov et al., 2010; Komeima et al., 2006; Rogers et al., 2007; Shen et al., 2005; Usui et al., 2009b). Rod cells have two major and highly compartmentalized functions related to vision: light detection in its posterior outer segments and synaptic terminal neurotransmitter release at its anterior pole; the extracellular space surrounding the outer segments [i.e., the sub-retinal space (SRS)] is also a key compartment for maintaining a healthy dark current and visual cycle (Adijanto et al., 2009; Cao et al., 1996; Li et al., 1994b).

Diabetic retinopathy (DR) and retinitis pigmentosa (RP) are two major diseases of the retina characterized by irreversible anatomical changes, deterioration of vision, and ultimately blindness (Campochiaro et al., 2015; Kern et al., 2010; Punzo et al., 2012). Current treatment options are either destructive and sub-optimal for DR (e.g., panretinal photocoagulation) or non-existent for RP (Campochiaro et al., 2015; Kern et al., 2010; Punzo et al., 2012). Rod cell-based oxidative stress has been implicated as a common pathogenic event underlying eventual histopathology in DR and RP, among other retinopathies (Fig. 1) (Cingolani et al., 2006; Dong et al., 2006; Du et al., 2013; Kassen et al., 2009; Komeima et al., 2006; Rogers et al., 2007; Shen et al., 2005; Usui et al., 2009b). A likely source of rod cell oxidative stress is the ellipsoid region of the inner segment which contain ~75% of retinal mitochondria (Johnson, Jr. et al., 2007; Medrano and Fox, 1995; Perkins et al., 2003). Notably, other abnormalities in, for example, DR, such as inflammation, appear as downstream consequences of oxidative stress (Du et al., 2013). In addition, the identification of rod cells as the main contributor to retinal oxidative stress complicates interpretation of systemic treatments that were previously thought to correct primarily endothelial cell oxidative stress.

These considerations provide a rationale for focusing on the evaluation of anti-oxidant therapy on rod cells *in vivo*. Much better outcomes in DR and RP can thus be expected if antioxidant therapy is started before gross changes are evident. However, testing the effectiveness of an antioxidant against rod oxidative stress has mostly relied on post-mortem studies and/or observing improvements in animal models following (often pleiotropic) anti-oxidant therapy (Berkowitz et al., 2007c, 2012a, 2009b; Campochiaro et al., 2015; Du et al., 2013, 2015; Fukuda et al., 2014; Galbinur et al., 2009; Jaliffa et al., 2009; Komeima et al., 2006; Rohrer et al., 2004; Sanz et al., 2007; Usui et al., 2009a; Yang et al., 2007; Zeng et al., 2014; Zheng et al., 2007). Such approaches i) are often unable to determine whether oxidative stress in rod cells *per se* has been corrected, and ii) are not useful for examining the same animal over time or for examining rod cell oxidative stress in patients. A need remains to non-invasively measure the efficacy of anti-oxidant therapy against early rod cell compartment-specific oxidative stress in diseases like DR and RP in order to personalize anti-oxidant therapy with regard to timing and dosing *in vivo*. In vulnerable neurons, including rod cells, one of the first consequences of pathogenic oxidative stress is cell dysfunction [e.g., (Du et al., 2013, 2015; Mao et al., 2014; Roddy et al., 2012; Wang and Michaelis, 2010)] (Fig. 1). Thus, we have focused this review on efforts on developing an optimized imaging platform that can non-invasively measure the effectiveness of antioxidant treatment in correcting rod cell compartment-specific pathophysiology before the appearance of other clinical biomarkers in disease.

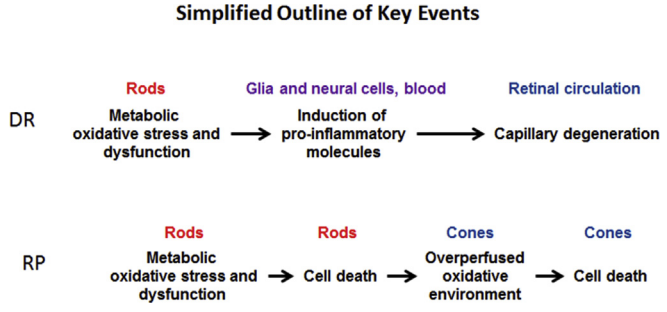

Fig. 1. Simplified representation of key events in DR and RP over time; DR and RP time courses are not to scale and are not comparable. The key point here is that rod cell metabolic oxidative stress and dysfunction – either from a metabolic disturbance (DR) or genetic abnormality (RP) – are important early events.

1.1. Problems with current technology

Conventional non-invasive approaches measure either blood vessel/flow (optical coherence tomograph (OCT) angiography, fluorescein angiography), anatomy (fundus photography, OCT, adaptive optics), or a global function (ERG). Behavioral tests (e.g., optokinetic tracking) examine whole-animal visual performance (e.g., acuity and contrast sensitivity) usually under phototopic conditions. Thus, these common approaches do not measure the package of rod-specific functions together with retinal vascular and choroid functions that are specifically evaluated by MRI (see below).

At present, OCT is the gold-standard for evaluating anatomical changes in the laminar structure of the retina *in vivo* but provides little functional information especially about rod cells. The most common method for evaluating rod photoreceptor function *in vivo* is the electroretinogram (ERG), which measures an integrated panretinal signal. Several studies have used ERG used to evaluate anti-oxidant therapies on diabetes-induced rod dysfunction, however, ERG reports on the entire retina and thus provides no panretinal spatial resolution (Barile et al., 2005; Horio et al., 2004; Johnsen-Soriano et al., 2008; Midena et al., 1989; Samuels et al., 2012). Multi-focal ERG (mfERG) can distinguish electrical responses from different regions panretinally but suffers from extensive light scattering in small rodent eyes (Ball and Petry, 2000; Nusinowitz et al., 1999). In other words, electrophysiology is a relatively insensitive tool for evaluating focal dysfunction in common preclinical models. ERG measures an important but limited aspect of