Molecular Aspects of Medicine 33 (2012) 399–417

Contents lists available at SciVerse ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

Consequences of oxidative stress in age-related macular degeneration

Stuart G. Jarrett [a], Michael E. Boulton [b,*]

[a] Department of Molecular and Biomedical Pharmacology, College of Medicine, University of Kentucky, Lexington, KY, United States
[b] Department of Anatomy and Cell Biology, College of Medicine, University of Florida, Gainesville, FL, United States

ARTICLE INFO

Article history:
Available online 9 April 2012

Keywords:
Retina
Age-related macular degeneration
Oxidative stress
Mitochondria
Reactive oxygen species
Antioxidants
Cell regeneration

ABSTRACT

The retina resides in an environment that is primed for the generation of reactive oxygen species (ROS) and resultant oxidative damage. The retina is one of the highest oxygen-consuming tissues in the human body. The highest oxygen levels are found in the choroid, but this falls dramatically across the outermost retina, creating a large gradient of oxygen towards the retina and inner segments of the photoreceptors which contain high levels of polyunsaturated fatty acids. This micro-environment together with abundant photosensitizers, visible light exposure and a high energy demand supports a highly oxidative milieu. However, oxidative damage is normally minimized by the presence of a range of antioxidant and efficient repair systems. Unfortunately, as we age oxidative damage increases, antioxidant capacity decreases and the efficiency of reparative systems become impaired. The result is retinal dysfunction and cell loss leading to visual impairment. It appears that these age-related oxidative changes are a hallmark of early age-related macular degeneration (AMD) which, in combination with hereditary susceptibility and other retinal modifiers, can progress to the pathology and visual morbidity associated with advanced AMD. This review reassesses the consequences of oxidative stress in AMD and strategies for preventing or reversing oxidative damage in retinal tissues.

Contents

* Corresponding author. Tel.: +1 3522738546; fax: +1 3528461248.
E-mail address: meboulton@ufl.edu (M.E. Boulton).

0098-2997/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mam.2012.03.009

1. Introduction

The retina resides in an environment that is primed for the generation of reactive oxygen species (ROS) and resultant oxidative damage. The retina is one of the highest oxygen-consuming tissues in the human body (Yu and Cringle, 2005). The highest oxygen levels are found in the choroid, but this falls dramatically across the outermost retina, creating a large gradient of oxygen towards the retina and inner segments of the photoreceptors which contain high levels of polyunsaturated fatty acids. This micro-environment together with abundant photosensitizers, visible light exposure and a high energy demand supports a highly oxidative milieu. However, oxidative damage is normally minimized by the presence of a range of antioxidant and efficient repair systems. Unfortunately, as we age oxidative damage increases, antioxidant capacity decreases and the efficiency of reparative systems become impaired. The result is retinal dysfunction and cell loss leading to visual impairment. It appears that these age-related oxidative changes are a hallmark of early age-related macular degeneration (AMD) which, in combination with hereditary susceptibility and other retinal modifiers, can progress to the pathology and visual morbidity associated with advanced AMD. This review reassesses the consequences of oxidative stress in AMD and strategies for preventing or reversing oxidative damage in retinal tissues.

2. Generation of reactive oxygen/nitrogen species

2.1. Reactive oxygen and nitrogen species

ROS and reactive nitrogen species (RNS) are highly reactive molecules acting in concert to modify proteins, nucleic acids, carbohydrates and lipids, often resulting in dysfunction of the biomolecule (Gutteridge and Halliwell, 2000) (also see reviews by Mettu and Sparrow in this issue). ROS and RNS are terms that commonly define either a free radical (i.e. a species that contains one or more unpaired electrons in the outer molecular orbitals), powerful oxidizing agents (e.g. hydrogen peroxide (H_2O_2) or peroxynitrite ($ONOO^-$)) or a species that exists at a higher energy level (e.g. singlet oxygen; $^1O_2$). At a physiological level, ROS and RNS can function as signaling molecules in crucial regulatory pathways including cell proliferation, gene expression and apoptosis (Leonarduzzi et al., 2011). However, ROS/RNS levels above physiological, or an imbalance in the oxidant/antioxidant ratio, can have significant pathophysiological consequences (Gutteridge and Halliwell, 2000).

The cascade of oxygen radical production begins with a single electron reduction of molecular oxygen (O_2) to form superoxide anion ($O_2^{\cdot -}$), which dismutates in the presence of either superoxide dismutase 1 or 2 (SOD1/2) into H_2O_2 and $O_2^{\cdot -}$ ($2O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2 + O_2$). One of the most destructive ROS, the hydroxyl radical ($OH^{\cdot}$), is formed through an iron-catalyzed Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^-$). Although $O_2^{\cdot -}$ is orders of magnitude less reactive than $OH^{\cdot}$, its reaction with nitric oxide (NO) forms the highly reactive oxidizing agent, peroxynitrite ($NO + O_2^{\cdot -} \rightarrow ONOO^-$). Lipid radicals ($L^{\cdot}$, $LO^{\cdot}$, and $LOO^{\cdot}$) are also generated via lipid peroxidation initiated by a ROS-induced hydrogen atom abstraction from a C–H bond of lipid. The half-lives of ROS/RNS vary from nanoseconds for the most reactive ROS (e.g. $OH^{\cdot}$) to minutes for rather stable oxidants (e.g. H_2O_2) (Winkler et al., 1999).