

Superoxide Dismutase Dysregulation Undermines Endogenous Antioxidant System and Promote Retinal Neurodegenerative Pathology

Vivek K. Gupta, Veer B Gupta

Vivek K. Gupta, Faculty of Medicine and Health Sciences, Macquarie University, 75 Talavera Road, Sydney, NSW 2109, Australia
Veer B Gupta, Centre of Excellence for Alzheimer's Disease Research & Care, School of Medical Sciences, Edith Cowan University, Joondalup, WA 6027, Australia

Correspondence to: Vivek K. Gupta, Faculty of Medicine and Health Sciences, Macquarie University, 75 Talavera Road, Sydney, NSW 2109, Australia

Email: v.gupta@ecu.edu.au

Telephone: +61-2-98502760

Fax: +61-2-98502701

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ABSTRACT

Oxidative stress is generally associated with unregulated relationship between free radical production and enzymes responsible for clearing them. Endogenous antioxidant system protects various tissues and cells rendered susceptible to damage by exposure to excessive oxidative milieu. Superoxide dismutase is one of the major enzymes in living systems to regulate endogenous reactive oxygen species (ROS) levels. It partitions highly reactive superoxide radicals into less damaging oxygen or hydrogen peroxide (H₂O₂). Glutathione peroxidase and catalase are some of the other enzymes which play significant roles in maintaining the equilibrium of free radicals and further decompose H₂O₂. Catalase mediates decomposition of hydrogen peroxide into O₂ and H₂O while glutathione peroxidase catalyses reduction of lipid hydroperoxides and hydrogen peroxide to H₂O. In the eye, ROS has particularly been implicated in mediating damage to retinal cells and other ocular tissues in diseases such as ocular hypertension, age related macular degeneration (AMD) and various inflammatory disorders of the eye.

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Key words: Reactive oxygen species; Superoxide dismutase; Age related macular degeneration; Intraocular pressure; Animal model; Retina

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EDITORIAL

Retinal tissue is metabolically highly active and as such is exceedingly vulnerable to reactive oxygen species (ROS) production. Various endogenous and dietary antioxidants have been shown to impart protection to the retinal neurons against oxidative damage^[1]. Susceptibility of biological macromolecules, retinal neurons and other ocular tissues to ROS mediated injury increases significantly in various retinal pathologies such as maculopathies, glaucoma and inflammatory disorders of the eye. Intraocular pressure is maintained by complex interactions between the aqueous humour and its transmission towards the posterior part of the eye globe including retina and optic nerve through vitreous humour. The rate of production of the aqueous humour and its drainage through the trabecular meshwork contribute to the overall pressure homeostasis inside the eye. Extra-ocular fluids such as arterial and venous blood pressure and intracranial pressure from the cerebrospinal fluid (CSF) also help to equilibrate this pressure in the eye^[2]. Variations in intraocular pressure can lead to several pathological conditions most of which are together grouped as heterogeneous group of diseases identified as glaucoma. Continuous exposure of the retinal ganglion cells (RGCs) and optic nerve to high pressure and accompanying oxidative damage leads to injury to the RGCs and the optic nerve^[3,4]. It is one of the leading causes of blindness and visual impairment worldwide. Age related macular degeneration AMD causes gradual

loss of the central vision by damage to the photoreceptors in the macular region and is often accompanied by accumulation of detrimental by-products such as lipofuscin, drusen and retinal pigment epithelium (RPE) atrophy which can be associated with neovascularisation in advanced stages^[5]. Antioxidant supplements, non-smoking and regular exercise have been shown to have protective effects against AMD damage. Although significant amount of research and resources have been dedicated to both glaucoma and age related macular degeneration (AMD) as well as biochemistry underlying associated retinal pathologies the exact pathophysiological mechanisms and targeted treatment strategies for these diseases still remain obscure^[6-8].

Several animal models have been identified to study the mechanisms underlying ocular hypertension and AMD. Studies have been carried out in monkeys, rabbits and rodent models-normal, inbred as well as transgenic^[9]. While several animal models of glaucoma and both dry and wet forms of AMD are available with varying degrees of disease representation, the complex pathophysiology of the diseases means that no single animal or cellular model is able to mimic the ocular hypertension/ glaucoma, AMD or other major retinal conditions as observed in humans. A possible strategy to diversify the approaches and push the research boundaries further could be to investigate the ocular changes taking place in the animal models which exhibit some of the changes associated with retinal diseases without actually being for example a typical primary glaucoma/ ocular hypertension or AMD model. Ocular hypertension, macular degeneration and other inflammatory disorders of the eye are all believed to expose the retinal and other tissues in the eye to oxidative stress mediated toxicity and resultant chronic irreversible injury. Superoxide dismutase is the enzyme that primarily helps in scavenging the reactive oxygen species (ROS) in the cells and tissues^[10]. Investigations into the eyes of superoxide dismutase ablated or mutant animals will help us to understand the involvement of exposure to ROS and accompanying oxidative stress on various ocular tissues especially the retina and optic nerve^[11].

Studies into this animal model will provide valuable information about oxidative stress mediated aspects associated with ocular hypertension, macular degeneration and other ocular degenerative and inflammatory changes. Since the mechanisms of damage and extent of degenerative injury differ widely with respect to various heterogeneities associated with the disease, human populations and ethnicities as well as in various models of the disease, this animal model will specifically be addressing the oxidative stress hypothesis including potential protection conferred by the superoxide dismutase from the retinal damage. It will also be able to shed light on the effects of inflammatory processes associated with various oxidative stress mediated ocular pathologies such as ocular hypertension/ normotensive glaucoma, photoreceptor degeneration and inflammation. In addition to several other manifestations such as nucleic acid damage, accumulation of advanced glycation end products (AGEs) etc. prolonged oxidative stress can also oxidise the methionine residues in various proteins such as serine protease inhibitors and inactivate them leading to uncontrolled proteolytic activation and this model will help to determine the role of tissue damage caused by uncontrolled proteolysis in the retina^[12]. These animals exhibit increased levels of circulating interleukin-6 and increased TNF α levels^[13]. Oxidative stress may contribute to mitochondrial swelling, disorientation, shortening, and disorganization of cristae 13 and mitochondrial aberrations are well known to play a role in several of the retinal degenerative diseases including glaucoma, age related macular degeneration (AMD) and

other optic neuropathies^[14]. Interestingly eyelid inflammation and changes in body fluids like tear and serum have also been observed in superoxide dismutase knockout animals^[13]. These animals depict accumulation of large lipid droplets in the acinar units of meibomian glands in old age. Exposure to oxidative damage may also lead to ocular surface epithelial cell damage^[13]. There is also a progressive loss of RGC density in the retina^[15]. The function of the RGCs was observed to be impaired in the pattern electroretinograms (PERG) recordings. These changes may also lead to secondary vascular changes caused by its effects on VEGF and its receptors and other factors regulating angiogenesis^[16]. However, it is to be recognised that these changes were not associated with primary pathology of ocular hypertension or other retinal diseases in these animals. Interestingly, these animals have also been shown to depict cochlear ganglion cell degenerative changes and decreased density^[17]. Experimental superimposition of this animal model with chronic and acutely elevated intraocular pressure conditions will further provide the opportunity of studying some of the changes associated with the ocular hypertension^[4]. Similarly, exposure of these mice to varying intensities of light stress or overlapping with other macular degeneration models will provide useful data about their susceptibility to photoreceptor degeneration and underlying mechanisms. Exacerbation of the degenerative changes in the eye especially the inner retina and optic nerve in response to exposure to varying degrees of elevated intraocular pressure and in the outer retina in response to light stress will highlight the role of oxidative stress in retinal diseases^[18]. This animal model will also be immensely useful in testing responses to various drugs and improve therapeutic strategies. It will also be of considerable importance in preclinical drug trials to study the effects of single or combination of antioxidants in retinal protection in various diseases in addition to the mechanistic value.

CONCLUSION

Long term exposure to reactive oxygen species can cause a significant damage to various parts of the eye including photoreceptors and other retinal neurons in maculopathies and ocular hypertension as well as various other inflammatory ocular pathological conditions. Intrinsic defence mechanisms provided by superoxide dismutase can provide considerable protection and superoxide dismutase knock out and mutant animal models can provide major insights into the role of oxidative stress in ocular hypertension, AMD and other retinal disorders. Future investigations should focus to clarify involvement of oxidative stress in retinal disorders by carrying out rescue experiments in transgenic animals and determining the association of genetic polymorphisms associated with antioxidant systems such as SOD in humans by carrying out clinical cross-sectional and longitudinal studies. Identification of the molecular mechanisms involved in oxidative damage will eventually help in the development of pharmacological and genetic targets for novel therapies to prevent and delay the progression of ocular pathologies.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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- Peer reviewers:** Tohru Yoshioka, Visiting Professor, Graduate Institute, Kaohsiung Medical University, 100, Shih-Chuan 1st Road, Kaohsiung, 80708, Taiwan.