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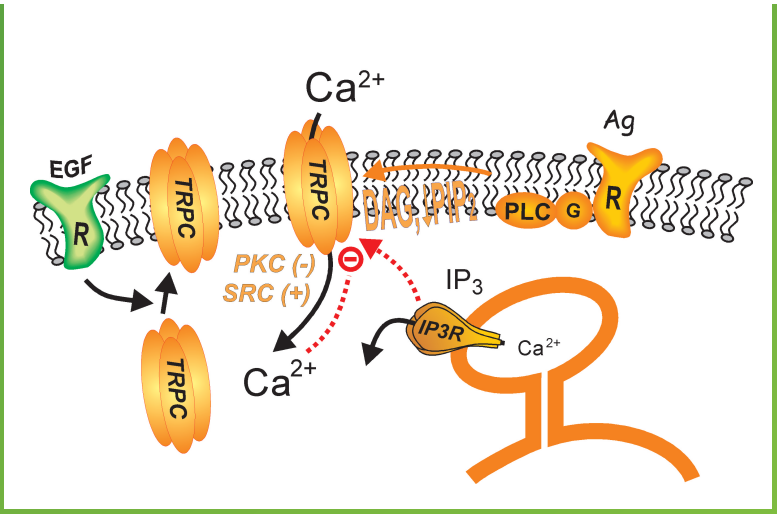

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Unifying Mechanism for Eye Toxicity: Electron Transfer, Reactive Oxygen Species, Antioxidant Benefits, Cell Signaling and Cell Membranes

Peter Kovacic,[1] Ratnasamy Somanathan[1],[2]
[1]Department of Chemistry, San Diego State University, San Diego, CA 92182-1030 USA
[2]Centro de Graduados e Investigación del Instituto Tecnológico de Tijuana, Apdo postal 1166, Tijuana, B.C.

ABSTRACT

Eye toxicity comprises an important part in the category of insults to major organs. There is considerable literature comprising industrial chemicals, atmospheric pollutants, metals, pesticides, therapeutic drugs, abused drugs and household chemicals. The list includes both endogenous and exogenous materials. The various constituents of the eye are affected. This review provides extensive evidence for involvement of oxidative stress (OS) and electron transfer (ET) as a unifying theme. Successful application of the mechanistic approach is made to all of the main classes of toxicants, in addition to large numbers of miscellaneous types. We believe it is not coincidental that the vast majority of these substances incorporate ET functions(quinone, metal complex, ArNO2, or conjugated iminium) either per se or in metabolites, potentially giving rise to reactive oxygen species (ROS) by redox cycling. Some categories, e.g., peroxide and radiation, appear to generate ROS by non-ET routes. Beneficial effects of antioxidants are documented extensively, in addition to literature on cell signaling.

Key words: eye toxins, electron transfer, oxidative stress, antioxidants, cell membranes.

Cell membranes play an important role, particularly the lipid constituents which undergo oxidation to toxic hydroperoxides. Recent literature is discussed which links pathogenesis of various eye components to toxicity resulting from oxidative injury to membrane lipids. Our framework should increase understanding and contribute to preventative measures, such as use of antioxidants. This review is the first to provide a comprehensive approach to the ET-ROS-OS mechanism. Also, it is unique in applying a multifaceted relationship to the toxicity mode of action.

INTRODUCTION

Extensive literature exists on the subject of eye toxicants which fall into various classes, such as industrial chemicals, atmospheric pollutants, metals, pesticides, therapeutic drugs, abused drugs, and household chemicals. The list includes endogenous and exogenous substances. The various constituents of the eye are affected resulting in adverse reactions ranging from minor irritation to permanent blindness. The preponderance of bioactive substances and their metabolites incorporate electron transfer (ET) functions, which, we believe, play an important role in physiological responses. The main groups include quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imines (or iminium species). In vivo redox cycling with oxygen can occur giving rise to oxidative stress (OS) through generation of reactive oxygen species (ROS), such as hydrogen peroxide, hydroperoxides, alkylperoxides, and diverse radicals (hydroxyl, alkoxyl, hydroperoxyl, and superoxide). In some cases, ET results in interference with normal electrical effects, e.g., in respiration or neurochemistry. Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range, i.e., more positive than -0.5 V. ET, ROS, and OS have been increasingly implicated in the mode of action of drugs and toxins, e.g., antiinfective agents (Kovacic and Becvar, 2000), anticancer drugs (Kovacic and Osuna, 2000), carcinogens (Kovacic and Jacintho, 2001a), and toxicants, namely reproductive (Kovacic and Jacintho, 2001b), hepatic (Kovacic et al. 2002), renal (Poli et al. 1989), cardiovascular (Kovacic and Thurn, 2005), neural (Kovacic and Somanathan, 2005), mitochondrial (Kovacic et al. 2005), abused drugs (Kovacic and Cooksy, 2005), ear (Kovacic and Somanathan, 2008), and various other categories including human illnesses (Halliwell and Gutteridge, 1999a).

There is a plethora of experimental evidence supporting the OS theoretical framework, including generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, and DNA oxidation and cleavage products, as well as electrochemical data. This comprehensive, unifying mechanism is in keeping with the frequent observations that many ET substances display a variety of activities, e.g., multiple drug properties, as well as toxic effects. Knowledge of events at the molecular level can result in practical application in medicine.

It is instructive to examine the basic biochemistry of ET functionalities in more detail. Redox cycling occurs between hydroquinone and p-benzoquinone, and between catechol and o-benzoquinone with generation of superoxide via ET to oxygen. Semiquinones act as intermediates. Various amino acids can operate

as electron donors. Superoxide serves as precusrsor to a variety of other ROS. The quinones can belong in either the endogenous or exogenous category. In the case of aromatic nitro compounds, the reduced nitroso and hydroxylamine metabolites can similarly enter into redox cycling, including an oxy radical intermediate. This class is only in the exogenous group. Less known are conjugated iminium compounds, of which paraquat is a predominant member (see below). Electron uptake yields resonance contributors. The imine precursor, commonly formed by condensation of protein primary amino groups with carbonyls, is readily converted to iminium by protonation. The metal category is treated in a section below.

This review demonstrates that the ET-ROS-OS unifying theme, which has been successful for many other classes of toxicants, can also be applied to eye toxicity. The toxic groups include a wide variety of structurally diverse substances. Not surprisingly, numerous reports exist on the beneficial effects of antioxidants (AOs). Cell signaling and cell membranes are also addressed. Our summary reveals that the mechanistic framework serves as a common thread for the large majority of reported toxins. This review is the only comprehensive, unifying and integrated one based on ET-ROS-OS, AOs and cell signaling. However, it should be emphasized that physiological activity of endogenous and exogenous substances is often complex and multifaceted. Our objective does not encompass extensive treatment of other modes of action. A number of original references may be found in the reviews and articles cited. The literature covered is mainly from more recent years.

POTENTIAL MECHANISMS OF EYE TOXICITY

Electron Transfer

A brief summary of the basic biochemistry of ET functionalities would be helpful as foundation for ensuing sections. Quinones undergo redox cycling with the corresponding hydroquinone or catechol with intermediate involvement of semiquinones (Kovacic and Becvar, 2000). A pertinent example is naphthoquinone (see Naphthalene section). A similar situation pertains to nitroso and hydroxylamine metabolites of ArNO2 involving intermediate oxy radicals (Kovacic and Becvar, 2000). A relevant example is chloramphenicol in the Therapeutic Drugs section. In some cases, the parent nitro compound is capable of electron uptake. For metal complexes, higher valence metals provide a large surface for electron delocalization and electron attraction by positive charge. Conjugated iminium species entail a similar electronic attraction and resonance stabilization via delocalization.

Reactive Oxygen Species and Oxidative Stress

There is extensive literature dealing with the toxic effect of ROS on various constituents of the eye. Glaucoma is associated with OS which contributes to pathogenesis and might be a target for prevention and therapy (Saccá et al. 2007). The ROS adversely affect the human trabecular meshwork (TM) whose integrity is compromised. There is correlation between oxidative DNA damage in the TM and visual field defects. The OS may contribute to homeostasis between NO and endothelins, with possible involvement in ganglional cell death. Furthermore, a genetic disposition may make for greater susceptibility to ROS damage. Evidence supports involvement of the immune system in glaucomatous neurodegeneration (Tezel et al. 2007). Findings support ROS regulation of the immune response by stimulating the antigen-presenting ability of glial cells and functioning as co-stimulatory agents for antigens. Increasing evidence points to a key role for ROS in this condition (Izzotti et. al. 2006a). Oxidative DNA damage is enhanced in the optical epithelium regulating aqueous humour out flow. The pathogenic role of ROS has implications for prevention (see AO section). There is increase in 8-OH-dG (8-hydroxy-2-deoxyguanosine) from DNA oxidative degradation in these patients (Izzotti et al. 2006b). Several lines of evidence support the pathogenic role of ROS, including the following items: (a) high levels of hydrogen peroxide, (b) TM possesses AO activity, (c) increases in SOD and GSH peroxidase activities in response to the threat by ROS, (d) ROS compromise TM integrity.

Reports provide considerable evidence in support of a role for ROS in cataract formation. Aging is by far the biggest risk factor for cataract (Truscott, 2005). Oxidation is the hallmark of this age-related illness. Loss of thiol groups and methionine oxidation increase as the condition worsens. There may be no significant protein oxidation in the lens center with advancing age. The key element in oxidative prevention appears to be the level of GSH. Evidence indicates that the lens barrier is importantly involved. About 25% of the population aged >65 years and about 50% aged >80 years experience a serious loss of vision from cataracts (Babizhayev et al. 2004). There is support for involvement of free radical-induced lipid oxidation in cataract development. Initial stages are characterized by accumulation of primary lipid peroxidation products, whereas in later stages there is prevalence of fluorescent end products. Oxidation of thiol groups results from a decrease in GSH. Data show that N-acetylcarnosine is effective in the management of cataract reversal, as well as prevention. Two major processes can occur with proteins in cataractogenesis (Davies, 2001). One involves direct photo-oxidation arising from UV radiation, thereby generating excited states or radicals. The other entails indirect oxidation

of protein by UV generated ROS. Mechanistic aspects are discussed. The phacoemulsification and asperation (PEA) technique has become the most popular cataract surgery (Takahashi, 2005). However, radical formation from ultrasound is believed to be a cause of corneal endothelium damage in PEA. In aqueous solution, ultrasound induces cavitation, resulting in generation of highly toxic hydroxyl radicals. The major ingredient in ophthalmic viscosurgical devices is hyaluronate, a free radical scavenger which is expected to provide protection against OS.

A related aspect comprises insult to the eye lens. Oxidative stress was induced in cultured lens epithelial cells and in intact mouse lenses by hydrogen peroxide (Petersen, 2007). The lenses exposed to the peroxide suffered loss of transparency, decreased proteasome activity and lowered GSH levels. Inhibition of proteasome in the cells produced increase in apoptosis and disturbed redox balance. Evidence was provided for involvement of an oxidative process by ROS that mediates apoptosis induced by transforming growth factor beta-2 in human lens epithelial cells (Yao et al. 2007). Results indicate redox regulation of lens epithelial cells (Wilhelm et al. 2007). Hydrogen peroxide and two AOs were used in the study. Both AOs completely inhibited proliferation.

Considerable work has been done on the relationships of OS to macular degeneration and retinal damage. New insights were recently provided on retinopathy which appears to be derived from OS (Hardy et al. 2005). Retinal tissue is rich in polyunsaturated fat which is sensitive to lipid peroxidation by ROS, and the tissue responds to pathogenic stimuli by activation of phospholipases that is the first step in the synthesis of important classes of lipid second messengers. There is discussion of the role of retinal oxygen metabolism in origin of macular degeneration (Nowak et al. 2005). The ROS are believed to be responsible for apoptotic cell death and development of pathological changes in the age-related macular degeneration. Many AO systems in the retina provide protection from damage by ROS. ROS appear to be involved in diabetic retinopathy (Yamato et. al. 2007). Evidence from ESR was obtained for free radical species in the eyes of mice with induced diabetes. Data are reported dealing with the effect of OS on mammalian retina (Yu et al. 2007). Oxidation reversibly inhibited phosphatase activity due to disulfide formation from Cys residues. Treatment with hydrogen peroxide caused an increase in phosphatase expression, as did constant exposure to light which induced photooxidative stress. Both oxidation and overexpression of phosphatase are enhanced by inhibition of the GSH AO system.

Various other articles deal with the subject of eye damage by ROS-OS. Oxidative stress from ROS is related to many chronic disorders, as pointed out in the Introduction, including cataracts and macular degeneration (Tsubota, 2007.). The ocular-surface is subject to OS from UV light, air oxygen changes in oxygen pressure due to blinking and inflammation. Mice deficient in SOD exhibited clinical aspects of macular degeneration. A case was reported of optic neuropathy related to inhalation of hydrogen peroxide (Doma□ et al. 2007). Evidence points to susceptibility of the ocular lens to tissue damage resulting from exposure to nitric oxide (Varma, 2007). Adverse effects include cataract formation. Another investigation also deals with NO-related cellular damage in the eye (Ozdek, 2007). Macular iron levels increase with age, which has the potential of contributing to retinal degeneration (He et al. 2007; Wong et. al. 2007). Post-mortem retinas from patients with macular degeneration have increased levels of iron. Compounds of this metal may play a role in a broad range of other ocular diseases, including glaucoma, cataracts and hemorrhage. Prevention by iron chelation has clinical potential. References to toxins in the Introduction discuss the action of iron as a Fenton catalyst in generation of toxic hydroxyl radicals from hydrogen peroxide. In addition to the adverse effects by ROS on the eye already mentioned, others include uveitis and retrolental fibrophasias (Ohia et al. 2005). Various peroxides exert toxic reactions of the anterior uvea, especially on sympathetic nerves and smooth muscles of the iris-ciliary bodies. Calcium and arachdonic acid metabolites appear to be involved. Effects caused by the peroxides in the retina are mediated by second messengers, such as NO. A variation in ocular perfusion may lead to an increase in ROS that could induce an apoptotic cascade in retinal ganglion cells (Haufroid and Collignon-Robe, 2004). An article puts focus on free-radical oxidation in the pathogenesis of eye diseases (Kravchuk, 2004). In addition to research already treated, there is a report on light-induced photoreceptor damage (Meyer-Rochow, 2001). A large number of variables are involved, including free radicals and lipid peroxides. The chemistry is discussed in more detail in a review on mechanism of carcinogenesis (Kovacic and Jacintho, 2001a.). A widespread endogenous source of ROS comprises the mitochondria which leak a small percent of electrons from the ET chain, resulting in formation of superoxide from reaction with oxygen (Kovacic et al. 2005). Various reports deal with the adverse effects of OS from ROS on eye constituents (Ottonello et al. 2000; Ohia et al. 2005; Moreno et al. 2004; Santosa and Jones 2005; Beatty, et al. 2000; Marsili et al 2004; Pradhan et al. 2004; Varma and Hegde, 2007; Spector, 1995; Seetharam and Sujatha,1998)

Reactive Nitrogen Species

The most important member is nitric oxide which is treated in a subsequent section. Peroxynitrite, formed

by reaction of NO with superoxide, can be beneficial or induce toxic effects (Jacintho and Kovacic, 2003). Aslan et al. (2006), using rat models of ocular injury, found that both elevated intraocular pressure and ocular inflammation augment inducible nitric oxide synthase (NOS2) expression, retinal protein nitration and apoptosis. Aslan et al. (2007) report that extensive formation of nitrated proteins and reactive nitrogen species in the cornea contributes to tissue destruction in uveitis. Hence, inhibition of NOS2 may have beneficial effects.

SURVEY OF EYE TOXICANTS

Ultraviolet (UV) Radiation

Normally, light transmission through the eye is benign. However, intense light exposure can be hazardous (Roberts, 2002, Roberts, 2001). Before middle age, there is protection by an efficient AO system. In addition, protective pigments dissipate energy. A brief review presents evidence that solar UV radiation increases the risk of several diseases of the eye, such as cataract and neoplasms (Gallagher and Lee, 2006). Various studies deal with cataract formation due to UV radiation (McCarty and Taylor, 2002; Ayala et al. 2000), involvement of free radicals, lipid peroxidation and protein modification (van Kuijk, 1991), as well as ROS formation and DNA damage (Wolf et. al. 2008). Recent investigations have been carried out on the adverse effects on the eye of increased exposure to UV radiation resulting from ozone depletion in the atmosphere (West et. al. 2005; de Gruijl et al. 2003). Radiation induces increase in ROS which can be countered by repair processes (Risa et al. 2004). Because of involvement by ROS in toxicity, research was carried out on AOs which were found to be beneficial (Karslioglu et al. 2005, Anwar and Moustafa, 2001; Fu et al. 2000). In other research, radiation induced proto-oncogene expression and cell death in ocular tissues (Wickert et al. 1999). In connection with other high energy radiation, laser eye therapy can generate ROS and RNS, which in turn initiate lipid peroxidation, protein damage or DNA modification (Mileva and Zlateva, 2005). Vitamin E supplementation reduces OS significantly.

ENDOGENOUS AGENTS

Some of these are discussed in earlier sections, such as ROS.

Nitric Oxide (NO)

This free radical serves a variety of functions in the body, including action as second messenger. The diverse effects involve vascular tone, neurotransmission, immune cytotoxicity and many others. A review deals with physiological and pathological functions, e.g., in the eye (Becquet et. al. 1997). Adverse influences are inflammation and degenerative diseases (glaucoma and retinal insult). The toxicity of NO is reviewed from the standpoint of ROS-OS (Jacintho and Kovacic, 2003).

4-Hydroxy-2-nonenal (HNE)

This toxin has attracted much attention as a degradation product of lipid oxidation. Cataract formation is associated with increased levels of HNE (Lassen et. al. 2007). More recently, the role of the more toxic 4-keto oxidation product has been addressed in relation to ET-ROS (Kovacic, 2006.).

Advanced Glycation End-products (AGE)

Formation of AGE is a key pathological event linked to a range of human diseases (Stitt, 2001). AGE are receiving attention as modulators of important visual disorders. Reports indicate widespread AGE accumulation at sites of ocular pathology. These products also induce apoptosis of bovine retinal pericytes (Denis et al. 2002). Treatment with various AOs completely inhibited apoptosis, suggesting involvement of OS. Other investigations associate AGE with generation of OS (Halliwell and Gutteridge, 1999c). The overall process entails formation of toxic ROS, such as hydrogen peroxide, superoxide and hydroxyl radical.

XENOBIOTICS

There are various reports dealing with large numbers or mixtures of eye toxicants, including common ones (McCaa, 1982.), environmental pollutants (Saxena et al. 2003; Jankauskien□ et. al. 2007), organic solvents (Gong et al. 2003), volatile chemicals (Doty et al. 2004), industrial chemicals (Gobba, 2003), and drugs and ocular toxicants (Chiou, 1999). Mode of action based on ET-ROS-OS is discussed in reviews on organ toxins in the Introduction. Individual members are addressed in the following treatment.

OTHER ENVIRONMENTAL TOXICANTS

Naphthalene

Naphthalene metabolites were examined in relation to lens cell toxicity (Russell et al. 1991).The quinone product was toxic to most cells and caused depletion of GSH levels. o-Naphthoquinone caused cortical cataract formation (Martynkina et al. 2002). Mitochondria in lens epithelial cells are the target of the toxicity. Oxidative stress has been implicated (Pandya et al. 2000). Apoptosis also occurs, which is attenuated by the AO curcumin. Additional discussion of OS via ROS from quinone metabolites is discussed elsewhere (Kovacic and Somanathan, 2005).

Styrene

Exposure of the eye to this polymer monomer im-

pairs color vision even at relatively low concentrations (Gong et al. 2002). Metabolites that may generate OS are the sidechain oxide and 4-vinylphenol (Kovacic and Somanathan 2006b).

Toluene

Authors concluded that impairment of color vision in industry can be chronic (Zavali et. al. 1998). Metabolic analogy has been drawn between benzene and toluene entailing hydroxylation as precursor to quinone formation (Kovacic and Jacintho, 2001a). The origin of ROS has been addressed, entailing hydroxylated metabolites, quinone methide and epoxide (Kovacic and Somanthan, 2005).

Ethylene Oxide

This reagent, widely used as an industrial intermediate for ethylene glycol, may produce cataracts (Fujishiro et. al. 1991). It is instructive that changes in the GSH redox cycle may be involved. A prior review documents the ability of alkylating agents to generate ROS (Kovacic and Osuna, 2000).

Sulfur Mustard

This chemical warfare agent mainly affects the eye, skin and pulmonary system (Vidan et al. 2002). Ocular injury is the most immediate and distressing. Inflammation and free radical formation are evidently involved (Morad et al. 2005). The poison causes destructive ocular lesions on the surface and cornea, leading to visual deterioration and irritation (Javadi et al. 2005). As in the case of the prior section, this chemical is an alkylating agent with the ability to generate OS (Kovacic and Osuna, 2000). DNA alkylation generates a conjugated iminium.

Methyl Methacrylate

In a study of this industrial monomer in the polymer industry, the following insults were observed: corneal edema, neurovascularization, iris engorgement, inflammation, limbal hyperemia and cataract (Holyk and Eifrig, 1979). The monomer resulted in depletion of liver GSH (Elovaara et al. 1983). It is proposed that activation occurs by oxidation to the 2,3-epoxy derivative (Boyland and Chasseaud,1967). Hence, the mechanism may be similar to that of the above alkylating agents.

Poynuclear Aromatic Hydrocarbons (PAHs)

Experiments with fish demonstrate an interaction between UV radiation and PAHs as a possible contributing factor to cataract induction (Laycock et al. 2000). Much research, particularly in the cancer and anticancer drug areas, reveal metabolism to an epoxide which functions as the toxic alkylator (Kovacic and Jacintho, 2001). Above sections address ROS formation.

Ethanol

There is increased risk of cataract formation from daily consumption of three drinks of alcoholic beverages (Prickett et al. 2004). On the other hand, there is decreased risk from intake of one drink daily. As discussed in a review, the higher risk may be attributed to enhanced production of ROS, whereas the beneficial effect may be due to AO action (Kovacic and Somanathan, 2006a).

Cyanide

Results with rabbits suggest that cyanide-induced cataractogenesis may be a consequence of disruption of vitreous human and lenticular Ca homeostasis (Okolie and Audu, 2004). Mitigation results from AO vitamin administration (Okolie and Asonye, 2004). Neurotoxicity is accompanied by increases in superoxide and lipid peroxidation (Kovacic and Somanathan, 2005). The adverse effects are attenuated by aspirin. Part of the pro-oxidant effect may reflect inhibition of AO enzymes, such as SOD and catalase.

Sulfur Dioxide

Various effects on the eye from inhalation exposure were examined (Kilic, 2000). Visual-evoked potentials are altered for which lipid peroxidation could play a role. There is potential for induction of protective AO enzymes. Decrease in activities of SOD and GSH was noted in studies as a heart toxin (Kovacic and Thurn, 2005). In water, sulfite is generated which is oxidized to radical anions of SO3, SO4 and SO5. Peroxidation of rat mitochondria can be induced by sulfite.

Anesthetics

Topical ocular anesthesia has been part of ophthalmology for more than a century (McGee and Fraunfelder, 2007). The most commonly used drugs are generally well tolerated, but can also be toxic to the eye, especially when abused. The most common insults are to the ocular surface, with others including corneal infiltrates, ulceration and perforation.

Therapeutic Drugs

There has been substantial research on this subject. The reports include various ocular toxic reactions brought about by a variety of therapeutic agents, including tamoxifen, retInoids, sulfa drugs, anticancer agents, aminoglycosides and antibiotics (Moorthy and Valluri,1999; Fraunfelder, 2003; Santaella and Fraunfelder, 2007; Abdollahi et. al. 2004; Li et al. 2008, Fraunfelder, 2006; Fraunfelder and Fraunfelder, 2004; Widmer and Helbig, 2006; al-Twei-

geri et al. 1996). Research on ocular toxicity has also centered on individual drugs, such as fluoroquinolones (Thompson, 2007), desferrioxamine (Blake et al. 1985), phenothiazine (Boet, 1970), 5-fluorouracil (Shapiro et al. 1985), chloramphenicol (Cole et al. 1957), chlorpromazine (Siddall, 1966), amphotericin B (Barza et al. 1985), radiosensitizer (Rootman et al. 1982), and carbencilline and gentamycin (Jain and Hussain, 1982). The unifying mechanistic framework for these drugs, based on ET-ROS-OS is available in reviews on anti-infective agents (Kovacic and Becvar, 2000) and anti-cancer drugs (Kovacic and Osuna, 2000).

Abused Drugs

Abuse of drugs, both legal and illegal, can cause ocular injury and disease (Mclane and Carroll, 1986). The drugs are grouped into five categories: opiates, marijuana, stimulants, depressants and hallucinogens. Cocaine is reported to cause corneal disrurbances ranging from superficial punctuate keratisis to perforation (Pilon and Scheiffle, 2006). The keratopathy may involve corneal epithelial disruption and stromal ulceration. A key cocaine metabolite is the nitroxide radical. A unifying mechanism for abused drug action and toxicity is proposed based on ET-ROS-OS (Kovacic and Cooksy, 2005).

Cigarette Smoke

Reports reveal strong association between smoking and common eye diseases, including Graves' ophthalmopathy, macular degeneration, glaucoma and cataract (Cheng et. al. 2000). It causes morphological and functional changes to the lens and retina, which can occur by direct contact or via the lung. There is enhanced generation of radicals and depletion of AOs. Ocular damage may lead to permanent blindness. Various studies deal with a link between smoking and cataract development, such as epidemiological data (Sulochana, 2001). Smokeless tobacco use was rather strongly associated with cataract (Raju et al. 2006). Decreased levels of the AOs, namely SOD, GSH and GSH peroxidase in lens of smokers suggests oxidative insult involved in cataract formation (Sulochana et al. 2002). Smoking produces deteriorating effects on the lipid layer of the ocular surface (Altinors et al. 2006). Cigarette smoke condensate causes OS and negatively affects detoxifying agents, such as GSH and GSH-S-transferase (Mathur et al. 2005). Various reviews in the Introduction deal with toxic components of smoke and their relation to ET-ROS-OS.

Pesticides and Herbicide

An association between retinal degeneration and fungicide use was observed among farmer applicators of pesticides (Kirrane et al. 2005). A recent review addresses ocular toxicity from pesticide application (Jaga and Dharmani, 2006). Exposure is related to retinopathy, neuropathy and abnormal ocular movement. Ocular surface toxicity resulted from paraquat accidentally introduced into the eyes of a fruit farmer (McKeag et al. 2002). The mechanism of these two classes in relation to the ET-ROS-OS approach is described in organ toxicity reviews presented in the Introduction.

Metals

Members of this class display various toxicities as presented in the references on toxins in the Introduction. Heavy metal compounds usually possess reduction potentials quite amenable to ET in vivo. Toxicity is characterized by generation of ROS, lipid peroxidation, DNA cleavage and decrease in AO concentration. The negative effects are alleviated by AOs of various types.

Some investigations on adverse effects of metals on the eye are presented herein. Exposure to soluble silver compounds may produce toxic effects on the eye (Drake and Hazelwood, 2005). Studies involving the effect of Cu, Zn and Pb on crab eyes revealed eye pigmentary abnormalities, particularly those involving the retina (Lavolpe et.al. 2004). The relationship between concentrations of Cu and Fe in the aqueous humour and intraocular pressure may help explain the role of these metals in the pathogenesis of glaucoma (Iqbal et al. 2002). Potential exposure of the eye to lead is a matter of concern resulting from use of certain cosmetics throughout the world (Nnorom et al. 2005). Their continuous use could produce an increase in the trace metal levels in the ocular system with accompanying toxic consequences. The levels of toxic metals (As, Cd and Pb) were significantly higher in scalp hair samples of children exhibiting ocular problems (Kazi et al. 2006). Administration of higher concentrations of zinc to the insulted retina exacerbates the condition and also acts as a toxin (Ugarte and Osborne, 2001). Zn supplements in the diet must be taken with caution. The effect of oral zinc on macular degeneration has been addressed (Newsome et al. 1988).

ANTIOXIDANTS AND EYE TOXICITY

A large amount of research, partly addressed in prior sections, has been carried out on the protective effect of AOs on eye injury, which lends support to involvement of ROS toxins in OS. Lutein and zeoxanthin, major components of macular pigment, are part of the retinal AOs (Chucair et al. 2007). In human retinal endothelial cells pretreated with hydrogen peroxide, clusterin protected against apoptotic cell death (Kim et al. 2007). A randomized clinical trial revealed a significantly lower incidence of age-related maculopathy in a cohort of patients treated with high doses of

AOs than in a placebo group (Algvere et al. 2006). Fruits and vegetables, a rich source of carotenoids and other AOs, are thought to provide health benefits by decreasing the risk of various diseases, including those of the eye (Krinsky, 2005, Guggenbühl, 2006). A randomized trial revealed a beneficial effect of AOs (beta-carotene, vitamin C and vitamin E) on slowing progression of age-related macular degradation (Evans and Henshaw, 2008). Supplementation by omega-3 polyunsaturated fatty acids is proposed for certain subjects at risk for age-related macular degeneration, and supplementation with an AO cocktail is recommended in other cases (Desmettre et al. 2004). Melanin can act as a photoprotector by quenching ROS (Dayhaw-Barker, 2002). In animal studies, AOs were found to inhibit retinopathy in diabetes (Kowluru and Kennedy, 2001). Increasing the diversity of AOs provides significantly more protection than using any individual AO. In an investigation of optical neuropathy, a decrease in GSH occurred with changes in thiol redox potential (Schoeler et al. 2006). Corneal damage occurs following exposure to ultrasound energy due to radical formation (Nemet et al. 2007). Addition of AOs, such as ascorbic acid, exerted a protective effect. A combination of high glucose and absence of SOD increases formation of cataracts (Olofsson et. al. 2007). Apparently, NO contributes to the process. L-Carnitine may protect against damage by gamma radiation by scavenging radicals and increasing SOD activity (Kocer et al. 2007). A similar protective effect was observed in the case of peroxide damage (Shamsi et al. 2007). 2-Cys peroxiredoxins are AO enzymes that eliminate hydrogen peroxide in the ciliary body of the eye, thus exerting a protective influence (Hong et al. 2007). Epigallocatechin gallate, an AO in green tea, attenuates damage to retina caused by ischemia/reperfusion and by hydrogen peroxide (Zhang et al. 2007).

Melatonin, endogenously produced in the eye, may act as a protective agent in ocular conditions, such as photokeratitis, cataract, glaucoma, retinopathy and ischemia/reperfusion injury (Siu et al. 2006). However, production of the AO is minimal in newborns, with gradual waning with aging. Supplementation may be beneficial. Influence on cataract formation and lipid peroxidation is in keeping with free-radical scavenging properties (Li et al. 1997). Results indicate that the AO may protect against UVB-induced cataract development by directly quenching lipid peroxidation (Bardak et al. 2000). Data indicate that melatonin has a promising role in the treatment of glaucoma (Lundmark et al. 2007). There are other studies relevant to the AO properties (Abe et al. 1994; Yağci et al. 2006)

Pathophysiological mechanisms involved in nutritional toxic neuropathies entail correction of OS and quenching of free radicals (Orssaud et al. 2007). An article deals with lipid peroxidation and AO defenses in eye diseases (Shaimova, 2002). A 2006 report addresses molecular mechanisms of neuroprotection in the eye (Barnsatable, 2006). A general discussion of AO mechanisms is available in a book chapter (Kovacic and Somanathan, 2006c).

Additional, relevant reports on AOs can be found in the following areas: Graves ophthalmopathy (Bouzas et al. 2000), ocular surface of diabetics (Peponis et al. 2002), association of ocular disorders with mortality (Clemons et. al. 2004), ageing macula (Gerster, 1991), diabetic retinopathy (Lin et al. 2006), photoprotectants (Stahl and Sies, 2005), radiation-induced cataracts (Karslioğlu et al. 2005), diabetes-induced cataracts (Osakabe et. al. 2004; Hegde and Varma, 2004; Kyselova et. al. 2005; Özmen et al. 2000), cataract and macular degeneration (Moeller et al. 2000), senile cataract (Miratashi et al. 2005), Behcet's disease (Taysi et al. 2002), eye tear fluid (Choy et. al. 2000), lipid membrane oxidation (Bhosale and Bernstein, 2005), ocular diseases (Boonefoy et al. 2002), retinal albumin leakage (Rota et al. 2004), retinal neurons (Lee et. al. 2001), ocular melanogenesis (Sarangarajan and Apte, 2004), retinal pigment epithelial cells (Lu et al. 2002), retinal cells (Areias et al. 2001), retinal neurons (Lee et al. 2001), ocular disease and visual dysfunction (Whatham et al. 2008) and cornea and conjunctiva (Demir et al. 2005).

CELL SIGANALING

A study demonstrates that pro-inflammatory cytokines increase ROS through mitochondrial and NADH oxidase in cultured human retinal pigment epithelial cells (Yang et. al. 2007). Because of the pathogenic role of cytokines, antagonistic cytokines have been tested with positive results in Grave's opthalmopathy (Marcocci, 2004). Antioxidant therapy might be envisioned since in vitro studies have shown possible involvement of ROS (Marcocci, 2004, Bartalena, 2003). There is a report on upregulation of the thioredoxin system via the Nrf2-AO responsive element pathway in adaptive-retinal neuroprotection (Tanito et al. 2007). In a study of retinoid signaling, results revealed that retinoic acid inhibits Ca elevation and over activation of calpains, suggesting the potential of calpain-targeting therapies for cataract (Nishikiori, 2007). The NF-kappa □ signal pathway may be important in hydrogen peroxide-induced damage in human lens epithelial cells that is involved in cataractogenesis (Jin et al. 2007). Data demonstrate selective induction of activated protein kinases (MAPK) in human lens epithelial cells by UV radiation (Bomser, 2002). These kinases modulate many cellular events, such as cell growth, death, differentiation and migration. Three major MAPK cascades have been identified. Prior work demonstrates the importance of kinase in cataract development. Activation of nuclear transcription factor in the retina of diabetics is inhibited by AOs,

suggesting involvement of ROS (Kowluru et al. 2003).

Considerable research has been done on the basic mechanism of cell signaling based on radicals and electrons. More than 10 years ago, ROS attracted attention in relation to cell signaling. Since then, several books have addressed this aspect (Forman and Cadenas, 1997; Hancock, 2005), including RNS, e.g., NO. Evidence has accumulated that ROS, such as hydrogen peroxide, superoxide, and the hydroxyl radical, are important chemical mediators that regulate the transduction of signals by modulating protein activity via redox chemistry (Veriweij and Gringhuis, 2002). Authors have proposed that ROS have been conserved throughout evolution as universal second messengers (Schulze-Osthhoff et. al. 1997). Nearly every step in signal transfer is sensitive to ROS, which can function as primary signals and as second messengers in the activation of transcription factors (Forman and Cadenas, 1997). The approach is elaborated in a recent review (Kovacic and Pozos, 2006). A 2004 review (Hormuzdi et al. 2004) summarizes the present status of electrophysiological effects and deserves special attention. After a burst of research dealing with electrical coupling, gap junctions became less popular among neurobiologists versus the ionic approach. Recent reports have brought gap junctions back into the spotlight, suggesting that this type of cell-cell signaling may be interrelated with, rather than an alternative to, chemical transmission. We believe the thesis is credible, since electromagnetic effects of electrons and radicals in motion should have an influence on positive and negative charges associated with the central nervous system (CNS).

Other studies have addressed the electrical framework (Kovacic and Pozos, 2006.). Results suggest that nanosecond-pulsed electric fields modulate cell signaling from the plasma membrane to intracellular structures and function (Beebe et al. 2003). This technology could provide a powerful, unique tool to recruit signaling mechanisms that can eliminate aberrant cells by apoptosis. A 1993 symposium (Frey, 1993) focused on bioelectricity of cell signaling. Living creatures can be regarded as complex electrochemical systems that evolved over billions of years. Organisms interacted with and adapted to an environment of electrical and magnetic fields. Humans are now immersed in a man-made environment of such fields whose long-term effects are unknown.

CELL MEMBRANES

There is extensive literature on the role of lipid peroxidation in toxicity. Cell membranes play an important part since lipids are essential constituents. Unsaturated lipid hydroperoxides comprise the principal actors that supply ROS. A toxic product from lipid degradation by ROS os 4-hydroxy-2-nonenal which has been the object of much research. Herein, recent examples are provided of application to eye membranes.

A study by Marin-Consta□o et al. (2005) showed that oxidant injury to human retinal pigment epithelial cells causes cell membrane blebbing. Apparently, oxidative attack disrupts the cell-specific surface proteases. Data by Yamada et al. (2008) support the hypothesis that oxidized lipoproteins comprise a trigger for initiating early events in the pathogenesis of age-related macular degeneration. The accumulation of certain lipoproteins in Bruch membrane evidently is involved. Oxidized LDL induced alterations in genes related to lipid metabolism, OS, inflammation and apoptosis. Florence (1995) noted that ROS cause lipid peroxidation in cell membranes and inactivate membrane-bound enzymes. These radicals that play a role in various diseases can be countered by use of AOs. In a recent report on oxygen toxicity in premature infants, Weinberger et al. (2002) invoked tissue injury by oxygen through formation of ROS which leads to peroxidation of membrane lipids. Protective measures include limiting oxygen and light exposure, as well as use of AOs and antiinflammaory agents. Evans et al. (1998) claim that linoleic hydroperoxide, an important source of biomembrane damage, is implicated in the onset of a variety of illnesses. A detoxification role for GSH peroxidase was indicated. Glutamate exposure, carried out by Mawatari et al. (1996), increased membrane oxidation two-fold, as judged by lipid peroxidation. ROS accumulate in response to OS after GSH depletion resulting in glioma cell death by Glu. Debbasch et al. (2001) discovered a significant decrease of membrane intergrety after exposure to quaternary ammonium salts. An apoptotic mechanism appears to be present. In this case, superoxide may play an important role in the tissue damage induced in the ocular surface disorders. In an investigation of action mechanism during OS-induced cataract, Spector (1995) observed damage to DNA and membrane pumps systems. Extensive oxidation of lens protein and lipid is associated with human cataract in older individuals and with the presence of elevated levels of hydrogen peroxide. Carmody et al. (1999) noted the ability of AOs to ameliorate light-induced retinal degeneration, suggesting a role for OS in cell death. Increase in ROS is accompanied by depletion in GSH in a model of photoreceptor apoptosis. These changes in cellular redox state precede disruption of mitochondrial transmembrane potential and DNA nicking that are events in apoptotic cell death. The ability of AOs to inhibit apoptosis through the scavenging of ROS establishes a role for ROS in photoreceptor apoptosis. In a report on uveitis, Goto et al. (1992) detected lipid peroxidation initiated by phagocyte-derived ROS. The presence of inflammation-mediated lipid peroxidation was confirmed by the generation of TBARS. Varma et al. (1984) examined the effect of OS on the lens and on cataract formation. Light induced lipid peroxidative degradation of tissue lipids.

The adverse effect was attenuated by scavengers of ROS. Lipid degradation was prevented by vitamins C and E. The results suggest that photodynamic injury to the lens and membrane lipids is incumbent upon initial generation of superoxide, followed by conversion to other ROS. Albender et al. (2007), in a study involving synaptosomal membranes, reported protection by melatonin against Al-induced oxidative damage, indicating a neuroprotective effect based on AO activity. In a related study (Karbownik et al. 2000), melatonin reduced the toxic effects of phenyhydrazine and iron in cell membranes, apparently due to beneficial AO action.

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