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Importance of Oxidative Stress in Ocular Dysfunction

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Purpose: This review illustrates an importance of oxidative stress caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation in association with eye disease, especially of cataract, and discusses an important role of lipid peroxide as a mediator of oxidative stress-related ocular dysfunction. **Methods:** Oxidative stress, resulted from the cellular production of ROS and RNS, is known to cause various forms of cellular damages such as protein oxidation, DNA breaks, apoptosis, and lipid peroxidation. These damages can be developed to human diseases. Accumulating evidence strongly suggests that continuous or constant exposure of eye tissues to oxidative stress is a main cause of cataractogenesis. Therefore, we investigated the action of oxidative stress in ocular dysfunction. **Results:** The ocular lens is continuously attacked by ROS inevitable generated from the process of cellular metabolism and the chronic exposure to ultraviolet. Excessive generation of ROS, resulting in degradation, oxidation, crosslinking and aggregation of lens proteins, is regarded as an important factor in development of cataract. **Conclusions:** These oxidative stress and oxidant/antioxidant imbalance produces the excess ROS which can lead to eye dysfunction. Even though known results, it should be noted that there is limited information on the molecular mechanism which can be better defined with the interrelation of oxidative stress and optic abnormalities.

Key words: oxidative stress, ROS/RNS, cataract, ocular dysfunction, lipid peroxidation

Introduction

Oxygen is essential to support aerobic metabolism and life. However, oxygen molecules undergo univalent reductions forming free radicals, single reactive oxygen species (ROS) and reactive lipid peroxidation products[1,2], due to reductive characteristics of normal cellular milieu. ROS are either byproducts of normal aerobic metabolism in mitochondria or second messengers in various signal transduction path ways[3,4]. They can be also derived from exogenous sources as a consequence of cell exposure to an environmental insult, or after being taken up directly by cells from the extracellular environment[4,5].

Oxidative stress is widely accepted as a major upstream component in the signaling cascade involved in many cellular function, such as cell proliferation, inflammatory response, stimulating adhesion molecules, and signal transduction[5]. Indeed, oxidative stress plays a key role in the pathophysiology of several major human diseases, including atherosclerosis, hypertension, heart failure, stroke and diabetes[6-8]. The accumulating evidence suggests that excess ROS involved oxidative stress plays an important role in the pathological process of many ocular diseases such as age-related macular degeneration, retinopathy of prematurity, retinal light damage, glaucoma, and cataract[9,10].

Oxidative damage, resulted from ROS due to light catalyzed reactions in the transparent ocular media, aqueous humor and lens, has been considered as a major factor in the development of cataracts[11,12]. According to recent studies[13,14], major factors responsible for ocular deteriorations are free radicals and oxidants, generated from external sources such as sunlight, ultraviolet (UV), toxins, drugs, and air pollutants as well as from internal endogenous sources to the lens epithelial cells. Because solar irradiation generates ROS, it is generally agreed that oxidative stress plays a major role in cornea and lens

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disorders[15-17]. ROS mediated oxidative damage involves a number of biological dysfunctions and can cause DNA damage, inflammation, collagen cross-linking, and lipid peroxidation[18-20].

The most abundant diffusible products of lipid peroxidation are chemically reactive aldehydes, such as malondialdehyde (MDA), acrolein, 4-hydroxynonenal (HNE) from the ω-6 fatty acyl groups, and 4-hydroxyhexenal (HHE) from the ω-3 fatty acyl groups[2]. Oxidative stress-induced lipid peroxidation in plasma or vascular tissues is a common occurrence in aging and age-related diseases. Increased oxidative stress produces several lipid peroxidation products that are intimately involved in the pathogenesis of cardiovascular diseases like atherosclerosis[21,22]. Recent studies illustrated a role of reactive aldehydes in nuclear factor kappa-B (NF-κB) activation and MAP kinase related-signaling pathways[23,24]. Previous studies underlay molecular course by which, in endothelial cells, oxidative stress-mediated the NF-κB activation mechanism elicited by reactive aldehydes. The mechanism might lead to vascular dysfunction by the activation of various proinflammatiry genes such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and xanthine oxidase (XOD)[23-25] (Fig. 1).

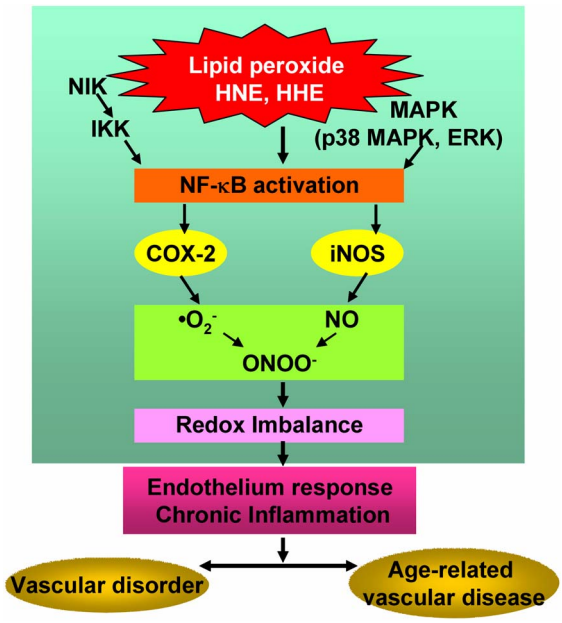

Fig. 1. Schematic presentation of reactive aldehydes on NF-κB activation in molecular inflammation involved vascular disorder. Reactive aldehyde induces the NF-κB transactivation by activating p38 MAP kinase and ERK and dependent on IKK resulting in up-regulation of the proinflammatory genes which lead to vascular dysfunction. ERK; extracellular regulated kinase. IKK; inhibitor kappa B kinase.

UV radiation induces lipid peroxidation in many cell types including human corneal epithelial cells[26]. UV radiation leads to the production of ROS, which initiates lipid peroxidation by attacking the polyunsaturated fatty acids in cell membrane phospholipids and eventually causes the accumulation of toxic and reactive aldehydes. Although reactive aldehyde acts as a potent mediator of ROS-induced oxidative stress, its precise roles has not been fully explored in eye disorders. This review summaries current evidence in which oxidative stress resulting from ROS generation has been associated with eye disease especially, cataract and speculates on the role of lipid peroxide as a mediator of oxidative stress-related ocular dysfunction.

ROS /RNS and Cellular Damage

For organisms living in an aerobic environment, their exposure to ROS and reactive nitrogen species (RNS) are continuous and unavoidable. For example, RNS, such as nitric oxide (NO) and peroxynitrite ($ONOO^-$), and ROS, such as superoxide (O_2^-), hydroxyl radical (OH), and hydrogene peroxide (H_2O_2), are widely implicated in age and age-related disease[27]. The deleterious characteristics of ROS/RNS depend on their concentration and the microenvironment in which they are released. Overproduced and/or unregulated ROS/RNS are major causative factors in tissue injury[28].

Among the various sources of ROS including NADPH oxidases, NO synthase (NOS), COX-2, and mitochondria[29,30], mitochondria is thought to be important since it is now becoming evident that the organelle can transduce a number of oxidative signals and impact on redox cell signaling[31,32]. Furthermore, recent study of Zmijewski *et al*. (2005)[33] reported that the generation of ROS from the endothelial cell, exposed to oxidized lipids, has a substantial mitochondrial contribution. Furthermore, recently Lee *et al.* (2006)[34] obtained data showing that mitochondrial dysfunction plays a key role in mediating HNE-induced vascular smooth muscle cells apoptosis through an increased mitochondrial production of ROS.

Accumulating evidence strongly indicates that ROS and RNS are widely implicated in the advanced aging[35,36] and chronic inflammation[35]. For instance, ROS are tumori-

genic by virtue of their ability to increase cell proliferation, survival and cellular migration that may relates to activation of activator protein-1 (AP-1) and NF-κB signal transduction pathways[37,38]. Previous studies done by Lee *et al.* (2005, 2004)[23,25] also demonstrated that aging and the age-related inflammatory process by NF-κB activation evolves through an oxidatively disrupted redox balance. Other studies further indicated that the increased activity of NF-κB from HHE treatment may strongly related to the oxidative status due to a shift in the intracellular redox balance[25,39].

Compared with unstable free radicals, $ONOO^-$ is a relatively stable species which can induce oxidation of thiol groups in proteins, nitration of tyrosine, and lipid peroxidation[21,40]. Indeed, $ONOO^-$ is known to play an important role in inducing cellular toxicity, affecting cell metabolism and signaling pathways[40]. In addition, alterations in NO production and $ONOO^-$ formation as well as ROS generation have profound effects on normal aging and disease conditions[36,42]. Therefore, the needs for effective $ONOO^-$ scavengers are important because of the lack of endogenous enzymes that protect against the damage caused by $ONOO^-$. Many antioxidants that are capable of quenching reactive oxygen have been tested for their capacity to affect ROS/RNS-mediated damage in cells[41]. In this study, I found that Zinjerone protects the ROS/RNS generation of keratinocyte in skin cells (Fig. 2).

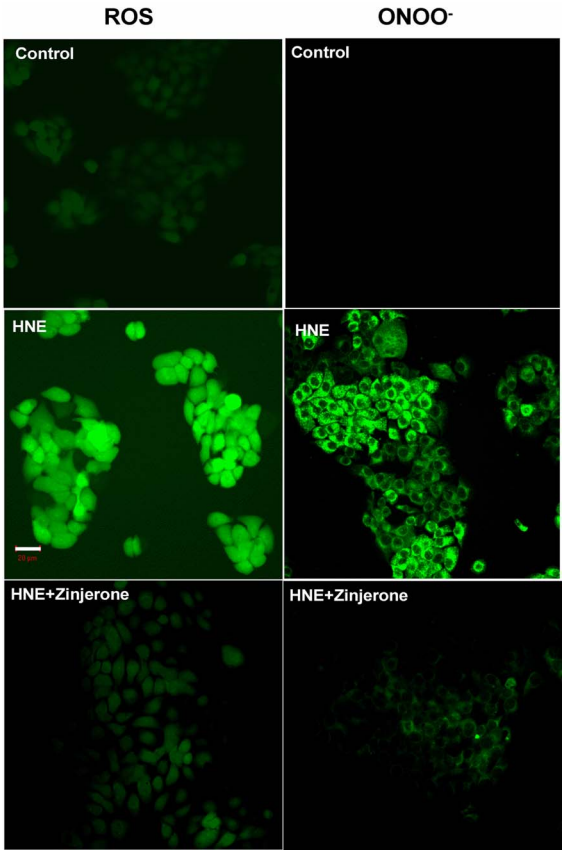

Fig. 2. The inhibitory effects of zinjerone on the HNE-stimulated ROS and $ONOO^-$ production. The cells were incubated in serum-free media with 10 μM HNE for 3 hr after pretreatment for 30 min with 500 μM zinjerone. Confocal laser microscopy analyzed the intracellular ROS and $ONOO^-$ levels with 2',7'-dichlorofluorescein diacetate (DCF-DA).

Factors Implicated in Optical Clarity

The eye is an elaborate sensory organ which receives visual information from the environment. It translates optical information into complex encoded electrical signals which are finally transmitted to the cortex for visual imagery. The visual efficiency primarily depends on the optical clarity of the eye (i.e. cornea, crystalline lens and intraocular media) and the neural integrity of the visual pathway (i.e. retina, optic nerve and visual cortex). It is well known that reduced optical clarity from a number of eye diseases resulted in decreasing visual efficiency (i.e. corneal dystrophies and cataract) or damaging neural integrity (i.e. age-related macular degeneration and optic neuritis).

Among human blindness worldwide, cataract, an opacification of the lens of the eye, is known as the leading cause of the one. ROS, generated as the by-products of cellular metabolism or the results of photochemical reactions, potentially targets the ocular lens. Constant exposure of eyes to high levels of solar radiation, specifically in the UV, provides an ideal environment for the generation of ROS in the ocular tissues[43,44]. Optical radiation is composed of different wave-length such as UV light (100~400 nm), visible light (400~750 nm) and infrared radiation (750~10,000 nm). The cornea absorbs most UV radiation below 295 nm, whereas UVB (280~315 nm) and UVA (315~400 nm) are blocked by the lens[44]. However, the combination of near continual exposure of the lens epithelial cells to UV radiation and molecular oxygen may lead to substantial oxidative stress and tissue damage.

Over 95% of the dry mass of the eye lens consists of specialized proteins called crystallins which connect to lens clarity[45,46]. When aged lens loss its clarity through

damage, cross-linking and precipitation of crystallins, aging of the eye lens lead to cataract formation. Damage to lens crystallins appears to be largely due to ROS and UV radiation. Whereas cross-linking reactions that produce insoluble aggregates, resistant to protease digestion, is primarily triggered by oxidatively denatured crystallins[45,47]. For example, reduced glutathione and ascorbate (Vitamin C) are one of antioxidants in the crystalline lens. Bardak *et al*. (2000)[47] demonstrated that melatonin, quenched free radicals and preserved antioxidant enzyme activities of the crystalline lens, could produce lower levels of oxidatively-damaged products in lens tissue under stress.

Oxidative Stress in Cataract Development

Oxidative stress is known to underlying mechanism of cataractogenesis. H_2O_2 exists naturally in the eye, however the levels of H_2O_2 in the aqueous and vitreous humor of human cataractous eyes are several times higher than in normal eyes[48]. Because H_2O_2 is quickly metabolized to the toxic, OH was considered as a principal cause of noncongenital cataract[48]. Kao *et al*. (2000)[49] found that the levels of NO in the aqueous humor are also elevated in patients with traumatic cataract, which suggests the involvement of $ONOO^-$ in this condition. Bhuyan *et al*. (1986)[50] and Chakrapani *et al*. (1995)[51] showed the evidence that elevated levels of peroxide in cataract due to oxidized glutathione concentrations of peroxide. Furthermore, Garner *et al*. (2000)[52] concluded that these findings are consistent with active roles of ROS and RNS in cataract formation.

It is also known that oxidative stress has been recognized as an important mediator of apoptosis in lens epithelial cells and also plays an important role in the pathogenesis of cataracts[45,53]. The lens exists in an environment in which endogenous sources of ROS is rich. This kind of environment are produced by the high local oxygen concentration, the chronic exposure to light, and the pathogenic activities of lens epithelial cells[54]. Although multiple physiologic defenses exist to protect the lens from the toxic effects of light and oxidative damage, mounting evidence suggests that chronic exposure to oxidative stress over the long term may damage the lens and predispose it to cataract development[44,45].

Exposure of lens to the sunlight and oxygen is highly associated with extensive damage to the long-lived lens proteins and other constituents. For example, Proteolytic systems recognize and selectively degrade oxidatively denatured proteins[54]. It has been established that oxidative damage to proteins increases with age in the eye lens[45]. Moreover, the young lens has substantial reserves of antioxidants (e.g Vitamin C and E, carotenoids), antioxidant enzymes (e.g. catalase) and glutathione reductase/peroxidase. Antioxidants may prevent oxidative damage of protein. In addition environmental stress including smoking and excessive UV-light exposure appear to provide an additional oxidative challenge associated with the depletion of antioxidants as well as with enhanced risk for cataract[55]. Superoxide dismutase (SOD) and glutathione are also critical enzymes that protect the epithelial cells in the lens from oxidative damage[56,57]. Taken together, it seems that oxidative stress and oxidant/antioxidant imbalance may play a pivotal role in optic abnormalities.

Lipid Peroxidation-mediated Cataractogenesis

UV-induced lipid peroxidation, protein modification, and extensive DNA damage can singularly or collectively lead to a death by apoptotic and necrotic pathways[58]. Lipid-peroxidation due to oxidative stress occurs in human cataract. Lens opacity has been found to be correlated with the level of reactive aldehydes, lipid peroxidation end-products accumulated in the lens[59]. In humans, compared to normal lenses, the level of reactive aldehyde was higher in well-developed cataractous lenses[60].

Correlating with an increase in lens opacity and changes in the refractive properties of the lens, these reactive aldehydes are implicated in human cataractogenesis because the toxic peroxidation products induce fragmentation of soluble lens proteins and damage vital membrane structures[59]. Interestingly, it has been recently reported that HNE can mediate oxidative stress-induced cell death in many cell types including lens epithelial cells[58]. DNA is also a target of increased oxidative stress, which has been shown to induce DNA damage and apoptosis in the epithelial cells in the human cataractous lenses[16]. Studies in rat lens in vitro suggest that the induction of apoptotic DNA fragmentation in lens epithelial cells could initiate lens opacification[61].

The mechanisms by which reactive aldehyde causes

lens opacification are not clear, but several possibilities can be considered. According to recent studies, HNE-mediated oxidative stress of the lens could be a causal factor in the cataractogenesis include in ubiquitin-dependent lysosomal degradiation, methionine sulfoxide reductase A, aldehyde dehydrogenase isozyme, and apoptosis of lens epithelial cells[61-64]. Because reactive aldehydes can form adducts with a number of biomolecules, including protein, nucleic acids, and some lipids, the deleterious effects of reactive aldehydes could offer the susceptibility of damage to eye molecules leading to ocular dysfunction.

Conclusion

Oxidative stress in animal cells implies increased oxidant production, characterized by the release of ROS, and which may cause cellular degeneration. The imbalance between ROS generation and the antioxidative defense system causes cellular damage leading to degenerative diseases in the eye including cataract. Chronic UV radiation mediated ROS formation is responsible for eye diseases. The ocular lens is a potential target of ROS, and ROS is generated as the by-products of cellular metabolism or the result of photochemical reactions. UV-induced Reactive aldehydes may exacerbate the weakened redox balance, which is leading to various ocular disorders. Oxidative damaged protein may play a critical role in the pathogenesis of cataracts. To understand potential role of lipid peroxide in eye lens further, a precise mechanism related to increase of modified protein that may cause ocular dysfunction should be determined.

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안구의 기능이상에 대한 산화스트레스의 중요성

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목적: 본 논문에서는 활성산소(reactive oxygen species, ROS)와 활성질소(reactive oxygen species, RNS)생성의 결과 초래되는 산화스트레스(oxidative stress)와 안질환과의 관계, 특히, 백내장발생과의 관련성 연구에 대한 고찰과, 안구의 기능이상에 있어 산화스트레스의 매개체(mediator)로서 과산화지질(lipid peroxide)의 역할에 대해 논의하고자 한다. **방법**: 산화스트레스는 단백질 산화, DNA 파괴, 세포사(apoptosis), 지질과산화(lipid peroxidation) 등의 다양한 세포손상을 나타낸다. 이러한 손상은 많은 질병의 발생과 관련되어 있다. 백내장 발생의 주요한 원인중의 하나가 안구조직이 일정하고 지속적으로 산화스트레스의 환경에 노출되는 것으로 알려져 있다. 따라서 산화스트레스의 안구기능이상에 대한 역할을 조사하였다. **결과**: 수정체는 자외선에의 만성적인 노출과 세포대사과정에서 필수불가결하게 생성되는 활성산소에 의해 끊임없이 공격을 받는다. 과도하게 생성된 활성산소에 의한 수정체 단백질의 분해(degradation), 산화(oxidation), 가교형성(crosslinking), 응집(aggregation) 등은 백내장발생에 있어 중요한 요인으로 사료된다. **결론**: 산화스트레스와 체내의 산화/항산화 불균형이 과도한 활성산소를 생성하게 되고 결국, 안구의 기능이상을 일으킨다고 할 수 있다. 이러한 결과들에도 불구하고, 산화스트레스와 안구이상과의 관계를 더욱 정확하게 설명할 수 있는 분자기전에 대한 정보는 아직 부족한 상태이며, 더욱 많은 연구가 필요하다.

주제어: 산화스트레스, ROS/RNS, 백내장, 안구 기능이상, 지질 과산화